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AN EXPERIMENTAL INVESTIGATION OF THE PHYSIOLOGICAL ACTION OF SALINE CATHARTICS,

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WITH WOODCUTS AND LITHOGRAPH.

EDINBURGH:
MACLACHLAN AND STEWART
(BOOKSELLERS TO THE UNIVERSITY).
LONDON: SIMPKIN, MARSHALL & CO.

MDCCCLXXXIV.

PRINTED BY NEILL AND COMPANY, EDINBURGH.

NOTE.

This Memoir was originally presented to the Medical Faculty of the University of Edinburgh as a graduation thesis for the doctorate, and gained for its author a gold medal, as also the Goodsir Memorial Prize. It was subsequently published, with a few alterations and additions, in Vols. XVI. and XVII. of the *Journal of Anatomy and Physiology*, and the present publication is a *verbatim* reprint from that Journal.

THE ACTION OF SALINE CATHARTICS.

By MATTHEW HAY, M.D., Edinburgh.

Of the various classes of cathartics in common use the saline have been the most recently introduced. Common salt, it is true, was occasionally employed as a purgative by the ancients, and probably the tartrates of potash were similarly used by Paracelsus and his followers; but it was not until the discovery of sulphate of soda by Glauber in 1658, named by him *sal mirabile*, that the attention of physicians was drawn to this class of cathartics. Five years later, the Duke of Holstein paid 500 thalers for the secret of the preparation of the long famous *sal polychrestus* or *tartarum vitriolatum*, a mixture probably of the neutral and the acid sulphates of potash. Seignette, an apothecary of Rochelle, prepared, in 1672, the double tartrate of potash and soda. Grew, in 1675, was the first to observe the presence of a purgative salt in the springs at Epsom, a salt which was afterwards shown by Dr. Black to be the sulphate of magnesia. Phosphate of soda was, in 1737, found in the urine by Hellot, and, some fifty years later, it was introduced into medicine as a purgative by Dr. Pearson. So that, by the commencement of the present century all the principal cathartic salts now in use had been discovered.

In a few of the works on the materia medica published towards the close of the last century, as those of Cullen and of Lewis, some attempt was made to indicate the manner in which the salts produced purgation; but, in the absence of experiment, and with a very imperfect knowledge of alimentary physiology, the opinions expressed are of little or no value. The first scientific explanation of their action was based upon the discoveries of Fischer and of Dutrochet,[1] who had demonstrated the remarkable physical property of salts known as osmosis. Poisseuille,[2] in a very ingenious monograph, believed to have found

[1] Dutrochet, *Recherches sur l'endosmose et l'exosmose*, Paris, 1828.

[2] Poisseuille, *Recherch. expériment sur les mouvements des liquides dans les tubes de petites diamètres*, Paris, 1828. *Comptes rendus*, t. xix. 1844, p. 94.

in this and other physical qualities of salts, and indeed of all drugs, a complete explanation of their action. That the purgative effect of salts was due to their endosmotic power was the most striking, and appeared the most satisfactory, of his numerous deductions. This view had been independently arrived at by Liebig,[1] but not stated with much certainty by him until 1848. Both had observed the osmotic action of salts in relation to blood-serum and to water, but neither had controlled their experiments by any on the living body. With what degree of care these observers, especially Poisseuille, arrived at this conclusion, may be gathered from the fact that, paying no heed to the irritant or specific action a purgative may possess, and absolutely regardless of what was long before known, that certain of the vegetable cathartics can act as efficiently when introduced into the blood as when administered by the mouth, Poisseuille ascribed the purgative action of even senna, colocynth, aloes, scammony, jalap, and castor oil to their endosmotic power, an application manifestly absurd.

Many other observers, working with much the same method and materials, signified their adherence to the view of Liebig and Poisseuille, in so far as it concerned the action of saline cathartics. The most distinguished among these was Mateucci,[2] who, in conjunction with Cima, has furnished physiological physics with some extremely ingenious and elegant experiments. Otto Funke,[3] and his pupil Krug,[4] from investigations with saline fluids and animal membranes, arrived at the same conclusion; and, much more recently, Rabuteau[5] has endorsed the opinion of these physiologists, since he has observed that the injection of a large dose of sulphate of soda into the circulation of a dog is followed by constipation rather than by purgation, while if the same dose be administered by the mouth purgation will ensue, showing that on whichever side of the intestinal mucous membrane the salt be placed there is an endosmotic flow of fluid towards it. Still more recently, Heidenhain,[6] from not having perceived the same effect follow the action of a solution of sulphate of magnesia on the glandular structure of the colon as when pilocarpin, a glandular stimulant, was introduced, has concluded that the salt causes "a simple endosmotic capillary transudation, and not a real glandular secretion."

Claude Bernard[7] was among the first to check the early progress of this too physical school. He strongly objects to the experiments and conclusions of Poisseuille, as making no allowance for the action of the

[1] Liebig, *Untersuch. üb. die Mineralquellen zu Soden u. Bemerk. üb. die Wirkung der Salze auf den Organismus*, Wiesbaden, 1839. *Ueber die Saftbewegung*, 1848.

[2] Mateucci, *Lectures on the Physical Phenomena of Living Beings*, translated by Pereira, 1847, p. 73.

[3] Funke's *Physiologie*, Leipzig, 1876, S. 237.

[4] Krug, *Nonnulla de theoria endosmos.*, etc., *Dissert.*, Lipsiæ, 1859.

[5] Rabuteau, *Mémoires de la soc. d. biologie*, 1868, p. 21. *L'union méd.* 1871, nos. 50 et 52. *Gaz. méd. de Paris*, 1879, 14 June.

[6] Heidenhain, *Physiologie d. Absonderungsvorgänge*, Hermann's Hdbuch. d. Physiologie, 1880, Bd. v. S. 172.

[7] Claude Bernard, *Substances toxiques et médicamenteuses*, 1857, p. 69, *et seq.*

nervous system and the mass of complex phenomena which constitute the living individual—"Partout où il existe de la matière, cette matière est soumise sans doute aux lois générales de la physique et de la chemie; mais, chez les êtres vivants, l'action de ces lois est étroitment liée à une foule d'autres influences qu'on ne saurait nier." Sugar, he says, whose endosmotic power is very high, should, according to the experiments of Poisseuille, act pre-eminently as a purgative. Bernard's criticism is, so far, thoroughly sound and justifiable; but when he proceeds to state, as an objection to Poisseuille's theory, that sulphate of soda purges when directly introduced into the veins, and even better than when swallowed, he makes an assertion which nearly all subsequent observers have failed to prove. As he quotes no experiments in its support, it is probable that he trusted to the statements of others, or to a common, but, as will be afterwards more fully shown, an erroneous belief. This inaccuracy does not, however, impair the correctness of his conclusions; he was seeking to establish general principles of medicinal action, not to discuss in particular the mode of action of a saline purgative.

The theory of the endosmotic action of the salt was more powerfully opposed by the experimental investigations of Aubert[1] and of Buchheim[2] and his pupil Wagner,[3] who clearly demonstrated that this theory did not offer a complete and satisfactory explanation of the purgative action.

Aubert, under the direction of Jolly, whose memoir on endosmotic equivalents has become classical, investigated the osmotic relation of various salts, diuretic as well as purgative, to blood-serum, with the result, that he ascertained that the salt with the highest endosmotic power is not the most purgative, as would have been expected were Poisseuille and Liebig's theory correct. Comparing three of the most important purgative salts, it was found by Aubert that phosphate of soda possessed an endosmotic power considerably more than twice as great as that of sulphate of soda, while the endosmotic equivalent of the latter salt was nearly thrice that of sulphate of magnesia; yet sulphate of magnesia is probably the most powerful cathartic of the three, and the phosphate is certainly the weakest. The inference is unavoidable that the endosmotic power of a salt is no indication, or, at any rate, not the sole measure, of its purgative strength.

From a few other experiments, Aubert concludes that the degree of concentration of the salt solution administered does not influence the degree of purgation, a point which I shall afterwards have to dispute. On the whole, he is inclined to ascribe the catharsis mainly to increased peristalsis, aided to some extent by the osmotic action of the salt.

Three years later, Buchheim, one of the greatest of modern pharmacologists, and whose death we had recently to deplore, conducted a series of experiments on himself and his pupil Wagner. In several instances they estimated the quantity of the purgative salt recoverable

[1] Aubert, *Zeitschrift f. rationelle Medicin.*, Bd. i. 1851, S. 93, u. 225.
[2] Buchheim, *Arch. f. physiolog. Heilkunde*, 1854, S. 93.
[3] Wagner, *De effectu natri sulfurici, Dissert. inaug.*, Dorpat, 1853.

from the urine after its administration in varying doses and degrees of dilution. They arrive at much the same conclusions as Aubert, and attribute to increased peristalsis—of which they did not, any more than Aubert, furnish direct proof—the principal action in purgation. They make the further suggestion, but equally fail to prove it, that the water of the stools is not the result of increased secretion from the intestinal mucous membrane, but rather the water in which the salt was dissolved when administered, or with which it came in contact in the alimentary canal. Their own experiments ought to have led them to an opposite conclusion; for on no occasion did they find that the concentration of the solution of the salt affected the activity of the salt. In contradiction of a single and unsatisfactory experiment of Aubert, they observed no purgation follow the injection of the salt into the circulation. In this they were supported by some experiments made in the same year by Donders.[1]

A few years previous to the investigations of these observers, the eminent chemist and physiologist, Carl Schmidt,[2] had advanced a new theory, or rather revived the theory of many of the older pharmacologists, that the salt excited, from the effect of local stimulation, a "transudation" through the capillaries of the intestine, which was neither an intestinal secretion nor an inflammatory exudation. He based this view upon the resemblance in chemical composition of the purgative stool to the choleraic dejection, the latter of which he believed to be produced in a similar manner. This theory has not met with much support, Radziejewski[3] and others having proved that it is untenable. By some, however, and even by so high an authority as Hoppe-Seyler,[4] and by those generally who do not believe that the existence of an intestinal secretion has been sufficiently demonstrated, it is still regarded as the most probable of the various theories advanced, as Schmidt's analysis of the purgative dejection agrees very closely with that of the serous transudation of dropsy.

To Headland,[5] at this time, are we indebted for a still more novel view of the action of the saline cathartic, a view which has been entirely ignored by all subsequent investigators. In his well-known work on the Action of Medicines, he had formulated a law, that all medicines pass into the circulation before they can exercise their action on the body; and, as a particular instance and proof of this, referred to the purgative action of certain salts. Misled by Aubert's paper, he wrongly assumed that these salts purge when injected into the blood, and unwarrantably deduced that only after absorption into the blood, when administered in the usual way, could they purge, the salts being absorbed by the stomach and upper part of the small intestine, and in the process of their elimination by the glands of the lower part of the

[1] Donders, *Physiologie d. Menschen*, Leipzig, 1859, Bd. i. S. 314.

[2] Carl Schmidt, *Characteristik d. epidem. Cholera*, Leipzig, 1850, S. 90, *et seq.*

[3] Radziejewski, "Zur physiolog. Wirkung d. Abführmittel," *Reich. u. Du Bois-Reymond's Archiv.*, 1870, Hft. i. S. 30, u. 67.

[4] Hoppe-Seyler, *Physiolog. Chemie*, 1878, Th. ii. S. 275, u. 358.

[5] Headland, *Action of Medicines*, 4th ed., 1867, p. 441, and p. 55, *et seq.*

small intestine exciting the secretion of these glands. This belief he founded upon three experiments on as many dogs, to each of which he administered a purgative dose (180 grains) of sulphate of magnesia. One he killed three-quarters of an hour afterwards; another in an hour and a half; and the third after two hours. By a somewhat imperfect method of analysis, the amount of the magnesia recoverable from the contents of the alimentary canal of each dog was estimated, and the corresponding quantity of sulphate of magnesia calculated, From the first dog he obtained fifty-six grains of the salt; from the second, seventy-seven grains; and from the third, ninety-seven grains. The conclusion appears unavoidable, that the salt is first absorbed and afterwards excreted. These experiments stand in opposition to the observations of all investigators since Headland's time, a single experiment by Carpenter[1] alone appearing to support them, purging having been produced when sulphate of magnesia was injected into the stomach with its pylorus ligatured. How far these observers are right, a large number of experiments of my own will determine.

In the same year in which Buchheim published his paper, Colin [2] made known a new method for ascertaining the action of a purgative salt on the intestine, a method which had been previously employed by Hunter, Magendie and others in the study of absorption, but not in determining the effect of purgatives. Moreau [3] did not make use of this method until many years afterwards, although to him is generally and wrongly ascribed its first employment. It consisted in making an incision into the abdomen of the horse (Colin) or dog (Moreau), exposing the intestine, into a loop of which, separated from the remainder of the gut by a couple of ligatures, was injected a strong solution of the purgative salt. As controls, a loop was ligatured off at each end of the original loop, and in these no salt solution was placed. In every instance they found that the salt solution had largely increased in bulk, while the adjacent controls remained perfectly empty. These two observers do not, however, agree as to the nature of the secretion. Colin regards it as a serous exudation; while Moreau maintains that it is a true *succus entericus*. The latter is of this opinion, because the fluid closely resembles that obtained by division of the mesenteric nerves supplying the loop, an experiment for which we are indebted to the ingenuity of Moreau.[4] Both fluids did not contain more than from 0·1 to 0·2 per cent. of albumen, a quantity much smaller than is met with in serous transudations. As many physiologists still doubt the existence of a true *succus entericus*, and as the proof of its existence and the capability of its rapid secretion is of the highest importance in solving the nature of purgative action, it is well to consider upon what grounds this fluid obtained by section of the mesenteric nerves can be regarded as a veritable intestinal juice, and not a mere serous transu-

[1] Carpenter's *Comparative Physiology*, 4th ed.

[2] Colin, *Physiologie comparée*, 1854, t. i. p. 649.

[3] Moreau, *Archiv. général, d. médecine*, VI. série, t. xvi. p. 234, 1870.

[4] Moreau, *Comptes rendus*, t. lxvi. p. 554; confirmed by Asp, *Ludwig's Arbeiten*, 1868; and Radziejewski, *op cit.* S. 41.

dation. Its chemical composition, as Moreau has pointed out, clearly supports this belief. Unfortunately, Moreau has not furnished us with an examination of its digestive properties. What these are will again be discussed. In the meantime, I would advance this further argument in favour of the fluid being a true secretion; that in the case of certain well-known secreting glands, as the submaxillary and sublingual salivary glands, and the pancreas, Bernard,[1] Heidenhain,[2] and Bernstein[3] have proved that a so-called "paralytic" but true secretion is produced by the division of all the nerves supplying these organs; why not from the intestinal follicles after division of the mesenteric nerves?

These experiments with purgatives, after the method of Colin and Moreau, have since been repeated with extreme care by Vulpian[4] and by Lauder Brunton,[5] by Böttger[6] in the laboratory of Bernstein, and by Brieger[7] at the suggestion and under the guidance of Cohnheim, and invariably with the same result—the excitation of a profuse secretion in the injected loop.

Lauder Brunton's experiments were professedly a careful repetition on the cat of those of Moreau and Vulpian, for the purpose of testing the accuracy of their results. He states his belief that the fluid secreted, on account of its containing little albumen, is a true intestinal secretion, and not a transudation.

Böttger, in his investigation, used frogs and rabbits. The secretion, which was copious, was, as obtained from the latter animals, mixed with blood, and yielded a large precipitate of albumen. He believed that the results of his experiments were best explained by the theory of Carl Schmidt, as the secretion possessed the composition of a transudation. He apparently overlooked the fact that blood is not usually present in the purgative stools of sulphate of soda, and that its presence in the fluid he obtained would sufficiently account for the large quantity of albumen.

Brieger improved upon the method of the others to the extent, that he washed out the loop of intestine before injecting the saline; so that the secreted fluid might be free from mixture with the remnants of partially digested food which were possibly present. The secretion obtained was yellowish in colour, and capable of digesting starch, and of dissolving raw fibrin, but was without action on boiled fibrin; it contained mucous and epithelial corpuscles, but no hæmocytes. The mucous membrane was pale and uncongested. The fluid, he concludes, s a true intestinal secretion.

[1] Bernard, *Leçons sur les propriétés physiol. etc. des liquides de l'organisme*, Paris, 1859.

[2] Heidenhain, *Stud. d. physiolog. Instit. zu Breslau*, Leipzig, 4 Hft.

[3] Bernstein, *Sitzungsb. d. Akad. d. Wiss. zu Leipzig*, 1869, S. 96.

[4] Vulpian, *Gazette médicale*, 1873, p. 300. *Leçons sur l'appareil vasomoteur*, t. i. p. 458, *et seq.*

[5] Lauder Brunton, *Practitioner*, vol. xii. 1874, pp. 342 and 403.

[6] Böttger, *Ueber d. physiolog. Wirkung d. Abführmittel. Inaug. dissert.* Halle, 1874.

[7] Brieger, *Arch. f. experim. Path. u. Pharm.* Bd. viii. 1878, S. 355.

Vulpian's investigation is one of greater length and complexity than those of the others, and requires a more extended notice, the more as he furnishes a new explanation of the action of the salt. He asserts that the salt neither excites a follicular secretion nor a dropsical transudation, but irritates the intestinal mucous membrane, causing an inflammatory exudation. The irritation, he believes, is not produced directly, but reflexly through a nervous mechanism involving the sensory nerves of the intestine, the various ganglia of the plexuses of Meissner and Auerbach, the solar and mesenteric plexuses, and even those of the lower thoracic nerves, and, finally, the vasomotor nerves. In opposition to this theory of Vulpian, I shall so far anticipate the results of my own experiments as to deny that the salt ever excites an inflammatory or catarrhal irritation of the intestinal mucous membrane, as judged from an examination of the membrane after it has been in contact with a solution of the salt, even so strong as twenty per cent.; and, as regards the involvement of a reflex nervous mechanism, it may be true, but it is quite devoid of experimental proof, if we except the experiment of Moreau, in which he showed the effect of the division of the mesenteric nerves on the intestinal secretion. Although the secretion is produced in this case by interference with the nerve supply, it does not necessarily follow that secretion cannot be excited by direct stimulation of the intestinal glands by the salt. Vulpian asserts that the fluid obtained by Moreau in this experiment is not intestinal juice, as it has not been shown to possess any digestive power, and is more fluid than the true juice. He apparently forgets that Radziejewski[1] found that it digested starch with ease, and dissolved albumen; and I do not know that more has been satisfactorily proved for the *succus entericus.* And, as to its fluidity, ordinary methods have failed to separate the juice in sufficient quantity and purity to enable us to form an opinion of the constancy and value of this character.

Besides experiments with purgatives made by the method of Colin and Moreau, Vulpian, through an incision in the abdominal wall, injected into the duodenum of the unligatured intestine of a dog a quantity of a solution of the saline; and an hour afterwards extended the incision upwards to the xiphoid cartilage, and downwards to the symphysis, and observed the appearance and movements of the intestine, as the salt solution passed towards the colon. On first exposing the gut, he noticed that the duodenum was reddened, and that gradually and slowly the jejunun and ileum became congested. This congestion he attributed to the action of the salt, but it was obviously due to the exposure of the delicate peritoneal surface of the intestine to the cold and dry atmosphere. Many investigators,[2] as well as myself, have had occasion to observe how quickly an inflammatory reddening suffuses the walls of the gut, when it is exposed to the ordinary atmosphere; one or two minutes are often sufficient. The conditions of the experiment are not good, and the results, therefore, untrustworthy.

[1] Radziejewski, *op. cit.* S. 45.

[2] Legros et Onimus, *Journ. de l'anatomie et physiolog.* 1869, p. 178. Houckgeest, *Pflüger's Archiv.* 1872, S. 266.

Vulpian also injected the sulphate of soda into the circulation, and obtained the same negative result as Buchheim, Wagner, Donders, and Rabuteau. In this he also agreed with Jolyet and Cahours,[1] who found from two experiments, likewise made on dogs, that neither the sulphate of soda nor the sulphate of magnesia purge when so injected. That is their conclusion, although they record that two liquid bilious stools were evacuated during the following night by the dog which received the latter salt.

In the course of his investigation, Vulpian, having become aware of some experiments by Luton,[2] in which the subcutaneous injection of small doses (1 decigrm.) of sulphate of magnesia in man was followed by purgation, repeated these experiments on dogs, and with a like result. He had previously ascertained that, curiously enough, a large dose (10 grms.) of sulphate of soda did not purge when so injected. Premising that the small dose is absorbed, and thereby produces its purgative effect, while forgetting that a similar dose injected directly into the blood will not purge, he proceeds to explain the negative result following the subcutaneous injection of the large dose as being due to its non-absorption, from the amount of inflammatory irritation and effusion it excites in the surrounding tissues; surely a fallacious assumption, as at least out of the 10 grms. injected, 1 decigrm., or one hundredth part, must be absorbed and pass into the circulation.

In the following year, Carville,[3] at Vulpian's suggestion, repeated these experiments on dogs, and, having injected subcutaneously a decigrm. of sulphate of magnesia, he killed the dogs before purgation had occurred. In all he found a catarrh of the whole intestine, the mucous membrane being congested and covered with a *sanguineous* effusion. This Vulpian supposes to thoroughly harmonise with his theory of inflammatory irritation; but, it is certainly remarkable that, while the absorption of a decigrm. will so greatly inflame the intestine, other investigators have never observed this condition follow the introduction of the salt in very much larger quantity into the alimentary canal, or its direct injection into a loop of the intestine.

Aubert, Buchheim, and Wagner I have already referred to, as assigning to excited peristalsis of the intestines the most important part in the production of saline catharsis. This is an opinion still very largely shared by German pharmacologists, especially since it has received apparent confirmation in Thiry's[4] well-known communication, and in the laborious investigation of Radziejewski.[5]

Thiry, whose work was carried out in the laboratory of Ludwig, employed a new and ingenious method for isolating a portion of the gut. He made an incision through the abdominal wall of a dog, and withdrew a loop of the small intestine, which, by dividing at its two

[1] Jolyet et Cahours, *Archives de physiologie*, 1869, p. 113.

[2] Luton, *Bulletin de la société méd. de Reims*, 1873, p. 126. *Gaz. hebdom.* 1874, p. 455.

[3] Carville, *Gaz. hebdom.* 1874, p. 405.

[4] Thiry, *Sitzungsb. d. k.k. Akad. d. Wissenschaft, Sitz.* 25 Febr. 1864, S. 19.

[5] Radziejewski, *op. cit.*

extremities, he completely separated from the remainder of the intestine, keeping, however, its mesentery intact. The continuity of the alimentary canal he restored by carefully joining with sutures the cut ends of the intestine. The isolated loop was then carefully closed by sutures at its one extremity, which was replaced within the abdomen, while the other extremity, kept patent, was sewn to the margins of the ventral wound. In those dogs, in which the operation succeeded, Thiry thus contrived to have a portion of the intestine free from contact with the aliment, and communicating with the outer air by an abdominal fistula, accordingly ready of access and easy of observation. No experiment was made until at least fourteen days afterwards, which time was required for the healing of the wounds.

Thiry's main object was to examine the nature of the *succus entericus*, which he hoped to have obtained abundantly by this method. In this he was disappointed; for the strongest mechanical irritation of the mucous membrane of the isolated loop did not yield him more than 4 grms. of secretion per hour from a loop 15 centimetres long. The injection of a strong solution of sulphate of magnesia equally failed to excite secretion. Thiry believed, from the latter experiment, to have furnished proof of Aubert's theory, that the salt does not stimulate the intestinal secretion, but acts by increasing the peristalsis.

There is, however, this serious objection to Thiry's method, that functional disuse of the fistulous loop for fourteen days or longer with the concomitant severe disturbance produced by the operation, in all probability, seriously impaired the secretory activity of the Lieberkühnian follicles. Even the few grammes of fluid obtained by mechanical irritation possess, according to Hoppe-Seyler,[1] exactly the characters of serum, and are, therefore, an inflammatory exudation, and not a true secretion. Schiff,[2] Leube,[3] Quincke,[4] Paschutin,[5] and Radziejewski[6] have repeated these experiments, and in every instance with a similar result. The last of these observers also administered a purgative dose of the salt *per os*, and collected the fluid which dropped from the fistula during the succeeding twelve hours. He found that, although free purgation had meanwhile occurred, there was no increase in the secretion from the isolated loop. If Thiry's method were trustworthy, Radziejewski's experiment would be opposed to the theory of Headland.[7]

Radziejewski conducted his investigation in the laboratories of Kühne and of Du Bois-Reymond, to the former of whom and Rosenthal he specially acknowledges his indebtedness for suggestions and assistance. As a result of his labours he has furnished us with the most comprehensive contribution that has as yet been made to this

[1] Hoppe-Seyler, *op. cit.* S. 275, u. 360.

[2] Schiff, *Nuove richerche sul potere digerente, &c.* Morgagni, July 1867, p. 5.

[3] Leube, *Jahresb. d. ges. Med.* 1868, S. 97.

[4] Quincke, *Archiv. f. Anatom. u. Physiolog.* 1868, S. 150.

[5] Paschutin, *Reichert u. Du Bois-Reymond's Archiv.* 1871, S. 305.

[6] Radziejewski, *op. cit.* S. 49.

[7] Headland, *supra*, p. 246.

discussion. It opens with a series of analyses, chiefly qualitative, of the fæces of the dog under normal conditions, and with a biliary fistula. He then proceeds to an examination of its composition after the administration of various purgatives, among others, sulphate of magnesia. Here he remarks that, with the exception of the increased proportion of water and the absence of indol, the stools are perfectly normal in composition, the albumen barely exceeding its usual quantity. From these facts and others he opposes strongly the theory of Schmidt —that the increase of fluid is due to serous transudation. The concluding sentence of his paper expresses this very distinctly—"die Entleerungen nach Abführmitteln sind Darminhalt, nicht Transsudat." Working with the object of proving that increased intestinal peristalsis is the principal factor, he frankly admits that his experiments, so far, do not positively prove it; for he expected to have found, had peristalsis been accelerated, that the fæces would have contained more partially digested food than they actually did.

The second part of his paper is occupied with an amplified repetition of Moreau's experiments on the effect of the division of the mesenteric nerves. In this he is not altogether very fortunate; for, in his first experiment, no secretion took place, although he had divided all the nerves entering the loop. A more careful examination at the autopsy revealed a few fibrils uncut. This is an experience which afterwards befell Vulpian,[1] and is of much interest and, I believe, importance, although neither observer draws any conclusion from it. Why does the copious secretion, following the division of the mesenteric nerves supplying a loop of intestine, not occur when a fibril or two escape section? The probable explanation seems to me to be that the mesenteric nerves not only inhibit secretion, but also excite absorption; and the latter process is, under the conditions of the experiment, in all likelihood, much more active than the former, so that the small part of the mucous membrane of the loop still retaining its mesenteric nerve-supply is capable of absorbing all the fluid that the remainder of the mucous surface can secrete. That nerves do exercise a considerable influence over absorption, the beautiful experiments of Goltz[2] have demonstrated; and why not in the intestine, where, *par excellence*, we would expect this influence to be manifest? The introduction of this view, according to which the quantity of the intestinal fluids is governed by two different sets of nerves,—those of secretion, and those of absorption, may seem somewhat out of place; but, as will afterwards be seen, it is of importance in considering the action of a purgative. For the salt may inhibit absorption as well as excite secretion, and thus doubly aid the accumulation of the fluid within the intestines.

In another experiment Radziejewski injected croton oil into a ligatured loop with its nerves undivided, and observed violent diarrhœa follow. This he believes to be due to reflex excitement of the peristalsis of the whole intestine, occasioned by the croton oil confined in

[1] Vulpian, *Leçons sur l'appareil vasomoteur*, t. i.

[2] Goltz, *Pflüger's Archiv*, Bd. v. S. 53.

the ligatured loop, forgetting, as his own protocol states, that the mucous membrane of nearly the entire length of the intestine was much congested, and the bowel above the ligatured coil distended with fluid, obviously an excited secretion. For neither of these conditions, of hyperæmia and hyper-secretion, could increased peristalsis account. Radziejewski was attempting to prove that excited peristalsis is the cause of all purgative action, and, in his eagerness to conform the results of his experiments to his theory, he clearly overstepped the limits of fair deduction. He did not inject a solution of a purgative salt into such a loop, and therefore omitted the experiment which operates most strongly against his theory.

Radziejewski closed his investigation with an examination of the time required by the food, with and without a purgative, to pass from the stomach to the cæcum, the latter having been rendered accessible by means of a fistula. Berries and crushed bones administered with sulphate of magnesia appeared at the cæcal fistula in much the same time as without the salt, but were preceded by a discharge of fluid. As a fact of practical value, he further observed that, especially after the administration of a drastic purgative, gastric digestion was completely arrested; pieces of meat, which had been eaten along with the purge some hours previously, were taken from the cæcum much in the same raw state as when ingested. The last of his numerous experiments consisted in watching the effect produced by the purge on the peristaltic movements; but he never could distinguish more than a moderate movement (mässiger Bewegung).

The researches of Thiry and Radziejewski present the main facts on which those who believe that purgatives act by accelerating intestinal movement base their opinion. I have given a perfectly unprejudiced account of the investigations of these observers; and I think it will be readily granted that such a conclusion is not warranted by the results of their experiments. Moreover, others as Legros[1] and Onimus, and Van Braam Houckgeest,[2] with suitable apparatus for observing and registering the movements of the intestines, and using certain precautions to avoid exposure of the intestines to the cold and dry atmosphere, have made a particular study of the effect of purgative and other salts on these movements, and are quite unanimous in their conclusions that the saline cathartic does not increase the intestinal peristalsis.

Among the most recent contributions to the subject of purgative action are those of Aguilhon,[3] and Laborde,[4] and a further communication by Rabuteau.[5] Aguilhon, in a study of the action of the purgative waters of Châtelguyon, has concluded that the active ingredient is chloride of magnesium; and this salt he has found by experiment to purge, whether injected into the stomach or into the blood. Laborde

[1] Legros et Onimus, *Journ. de l'anat. et physiol. de Robin*, 1869, p. 187.

[2] Houckgeest, *Pflüger's Archiv*, 1872, S. 266.

[3] Aguilhon, *Gaz. hebdom.*, 1879, p. 336.

[4] Laborde, *Gaz. hebdom.*, 1879, p. 352.

[5] Rabuteau, *Gaz. méd.*, 1879, No. 29.

has observed increased peristaltic movements follow the intravenous injection of the salt, but in no case purgation. Rabuteau denies that it is capable of producing either effect when so injected.

Professor Rutherford [1] has lately supplied us with the results of an exhaustive research on the action of a large number of substances on the secretion of the bile, and has shown that whatever effect saline purgatives may exert on the expulsion of bile from the gall-bladder, they do not greatly influence the bile secretion. Phosphate of soda, sulphate of soda, sulphate of potash, and Rochelle salt all slightly increased the bile secretion, whilst sulphate of magnesia diminished it. Generally, he has found that even in the case of powerful cholagogues, as podophyllin, the greater the purgative action, the less is the excitation of the biliary secretion. The bile does not, therefore, appear to be an important source of the fluid found in the intestines during the action of a purgative. Rutherford also observed the action on the intestines of the various cathartics after their injection into the duodenum. In the case of the purgative salts, his solutions were so concentrated, rarely less than fifty per cent., that they produced, as the autopsy revealed, considerable inflammatory irritation of the intestinal mucous membrane, a condition which does not follow the injection of a weaker solution, as I shall have occasion to point out. The intestinal fluid he obtained must, accordingly, have been largely mixed with an inflammatory exudation; and it is impossible to ascertain to what extent the increase of the intestinal fluid which he observed to follow the injection of the salt, was due to the presence of this exudation.

To complete the literature of this subject, I have yet to mention that Professor H. C. Wood [2] of Philadelphia has made the statement that section of the vagi prevents the action of the purgative, and ascribes this effect to some vaso-motor disturbance, believing that the vagi may antagonise the splanchnics, whose division is generally considered to be followed by dilatation of the blood-vessels of the intestine.

En résumé, it will be gathered from this sketch of the many attempts to solve the nature of saline purgation, that pharmacologists are very far from being agreed as to the nature of that action. There are some who maintain that the salt excites a flow of fluid into the alimentary canal, others who as confidently assert that it merely excites peristalsis.

Of the former, Liebig and Poisseuille, without venturing to speculate as to the exact nature of the fluid, believe that it is extracted from the blood through the capillaries of the intestine in virtue of the endosmotic power of the salt. Colin, Moreau, Lauder Brunton, Böttger, Brieger, and Rutherford conclude that

[1] Rutherford, *Action of Drugs on the Secretion of the Bile*, 1880.

[2] Wood, *American Journ. of Med. Sciences*, 1870, p. 395.

the fluid is probably intestinal juice, secreted under the local stimulus of the salt. Vulpian, on the other hand, regards it as an inflammatory exudation; while Schmidt calls it a transudation produced in the same manner as the choleraic discharge. Headland thinks that the salt, after being absorbed by the blood, stimulates Lieberkühn's glands in the process of its excretion. If this be so, why does the salt not purge when injected into the blood, as Buchheim, Donders, Rabuteau, and others have shown?

Of the latter, Thiry and Radziejewski are of opinion that the salt produces its effect by mere excitation of peristalsis; whilst Aubert, and Buchheim, and Wagner consider that the increased peristalsis is aided by the slow diffusibility or absorbability of the salt, and by the salt combining with the water of the alimentary canal to hinder its absorption. But Legros and Onimus, and Houckgeest could not perceive that the movements of the intestine were to the smallest extent stimulated by the presence of the salt.

Finally, the remarkable results obtained by Luton and Carville require to be reconciled with the experiments of the other investigators.

With the prevalence of so many theories and so much uncertainty as to the action of so commonly employed pharmacological substances as saline cathartics, there is ample justification for another effort being made to offer a more comprehensive and satisfactory explanation of their action. There is the further inducement to their study, that their action presents the key to the action of nearly all other purgatives, and to many common physiological and pathological phenomena. "If the action of sulphate of soda were known," wrote Buchheim at the conclusion of his paper in 1854, "it would help us to ascertain with greater precision the influence of other remedies on the body, for example, as a proof-stone for the remedies used to cure diarrhœa."[1] And after twenty years, by no means unfruitful in investigations of this action, Vulpian cannot more fitly introduce its discussion into his lectures than with the words, "Tout le monde parle de l'action des purgatifs, et, cependant, s'il y a une action encore peu connue, c'est bien celle de ces médicaments."[2] This, after the able

[1] Buchheim, *op. cit.* [2] Vulpian, *Leçons cit.*

investigations of Buchheim, Thiry, Moreau, and Radziejewski, is certainly no compliment to pharmacology. But the difficulties which surround such an investigation may well be the excuse for the paucity of its results. The very complex, and as yet very imperfectly understood nervous supply of the intestines, and the disturbance produced in experiments as those of Colin and Moreau by the mere exposure of the sensitive abdominal viscera, and, generally, the very unsatisfactory condition of our knowledge of the physiology of the intestines, have prevented previous observers from employing good methods of experimentation, and from drawing unassailable conclusions from their experiments. By repeating some of these experiments under new and varied conditions, I have endeavoured to estimate the true value of their methods, and by the adoption of new methods in which the normal state of the alimentary canal has been undisturbed by surgical operation, I have been enabled to obtain results, to which little or no objection can be offered. These I shall present in the form of several series of experiments, of which the following is the probable order, an order which, if in some respects more arbitrary than natural, approximates to that in which the experiments were made :—

Series, A.—The effect on purgation of the administration of the salt by the mouth in a state of concentration and of dilution; and the elimination of the salt by the kidneys and the alimentary canal.

Series, B.—The effect of the salt on the intestine when injected directly into the viscus, after the method of Colin and Moreau, with analyses of the fluid as to the salt it contained, and as to its digestive and other properties.

Series, C.—The effect of saline purgation on the concentration of the blood.

Series, D.—The effect of the salt on the alimentary canal, and its absorption from the canal, as ascertained by killing the animals at stated intervals after the administration of the salt by the mouth, and measuring the fluid in the canal, and estimating the quantity of the salt present.

Series, E.—Its purgative effect when injected into the blood.

Series, F.—Its purgative effect when injected subcutaneously.

Series, G.—Its effect on the circulation.
Series, H.—Its effect on the secretion of urine.

SERIES OF EXPERIMENTS, A.

The effect on purgation of the administration of the salt by the mouth in a state of concentration and of dilution; and the elimination of the salt by the kidneys and the alimentary canal.

Assuming that the method of Colin and Moreau[1] is open to objection on account of the violence done to the natural conditions of the intestines, and that the results they obtained in proof of a salt exciting secretion may be fallacious, and granting that Legros and Onimus, and Houckgeest[2] have succeeded in demonstrating that the purgative does not stimulate peristalsis, it is possible that the salt may produce purgation by merely uniting with the water with which it is administered, and the fluids with which it comes in contact in the alimentary canal; and itself being slowly diffusible, may prevent the too rapid absorption of the water with which it is united. This view was first suggested by Buchheim,[3] but coupled by him with stimulated peristalsis. This observer failed, however, to offer the slightest experimental proof of his suggestion. If a purgative salt does act in this manner, it is evident that, if it could be administered without, or with very little, water to an animal whose alimentary canal was rendered by some means free from fluids, no purgation would follow. For this purpose Buchheim and Wagner abstained from fluids for one day, and in the course of the same day ate each a full dose of the exsiccated sulphate of soda, yet purgation followed as usual. This did not deter these observers from still clinging to the view they had formed, believing, no doubt, that they had not sufficiently freed the alimentary canal from the fluids which are usually present.

While working under Professor Schmiedeberg in his laboratory at Strassburg, I was induced by him to test Buchheim's suggestion by a stricter method, and on the lower animals. And for much valuable and kindly-given help in carrying out this the first series of experiments, I very warmly acknowledge my great indebtedness to that distinguished pharmacologist.

[1] *Supra*, p. 5. [2] *Supra*. p. 11. [3] Buchheim, *op cit.*

The salt employed was mostly the sulphate of soda, and in a few experiments the corresponding compound of magnesia. The experiments were conducted on rabbits, cats, and dogs. In ascertaining the amount of the saline eliminated in the urine and in the fæces, every precaution was taken to ensure that the whole of these excretions were obtained, and that the method of analysis was exact and conducted with all care. With this object the animals were kept in the usual zinc boxes provided with an opening at their most dependent part for the escape and collection of the urine. In certain experiments, where great accuracy was desired, the urine of the dogs was removed by catheterisation, in order to prevent its being contaminated with fæces, and to obtain, by emptying the bladder, the whole of the urine excreted by the kidneys during a stated period. In estimating the quantity of sulphuric acid in the urine, the usual method of precipitation was followed.

A given portion of well mixed urine, the remainder being retained for a second, or even third, analysis, if that were necessary, was treated with excess of hydrochloric acid, and filtered, and the filter washed until the washings gave no trace of a precipitate with barium chloride. A solution of this salt was then added in slight excess to the filtrate, and the fluid containing the precipitate of sulphate of barium was placed for some hours over the water-bath, in order to consolidate the precipitate, and prevent its passing through the filter, as it was otherwise apt, to some extent, to do. It was now filtered, and the filter containing the sulphate was repeatedly washed with hot distilled water until the washings gave no opacity with sulphuric acid, or with nitrate of silver and nitric acid. This often occupied several hours. The filtrate was tested with barium chloride to make certain that all the sulphuric acid had been precipitated. The filter with the barium sulphate was dried in a steam-bath, and burned in a platinum capsule, the ash being rendered perfectly white, if that were necessary, by the addition of a drop or two of sulphuric acid, and again burning. Cooled in a dessicator and weighed, the amount of barium sulphate was obtained after deducting the weight of the capsule and the ash of the filter paper. From this was readily calculated the amount of sulphuric acid, or of sulphate of soda, to which the weight of the barium sulphate corresponded. In almost every case the analysis was controlled by a second, and if the results of the two materially differed —more than by 0·01 gramme—a third was made.

The analysis of the fæces was attended with more trouble. Two methods were open—either to digest the fæces with acid and water, and filter and wash, and estimate the sulphates from the filtrate, or to burn the fæces and estimate the sulphates in the ash. The former

method is the more correct theoretically, as in the latter, by the burning of the fæces, a certain amount of the sulphuric acid may be decomposed in the charring, or a slight excess obtained from the oxidation of the sulphur of the albumen. The latter is, however, much more practicable than the former, as owing to the large amount of mucin present in the fæces, many days will not suffice for its perfect filtration and washing. All my analyses were accordingly made by the method of combustion, employing for this purpose a powerful oven. Previous to burning, the quantity of water in the fæces was ascertained by heating them to perfect dryness over the water-bath, and afterwards in the air-bath at a temperature of 110° C.; and in order to prevent the volatilisation of acids a given weight of exsiccated carbonate of soda was sprinkled over the fæces before being placed on the bath. After burning, the ash was dissolved in hydrochloric acid and water, and the sulphuric acid of the filtrate estimated exactly as in the case of the urine.

I have described with minuteness these simple methods of analysis, in order to leave no room for doubt in the minds of others as to the accuracy of my work, as well as to do justice to the care with which the analyses were performed.

In all the succeeding experiments where the sulphate of soda is mentioned as being administered, the usual crystalline form of the salt ($Na_2SO_4.10H_2O$) was that employed.

Experiments on Rabbits.

Experiment I.—To ascertain the dose of sulphate of soda necessary to produce purgation, when administered in the form of a dilute solution.

Rabbit, weighing 1440 grammes. Injected into the stomach through a vulcanised catheter 2 grammes of the salt, dissolved in sufficient water to form a 10 per cent. solution. On following day, no purgation; injected 3 grammes (5 per cent. solution). At noon, next day, still no purgation; injected other 3 grammes (5 per cent. solution). Purgation followed in two hours afterwards—copious brown watery discharge. The short interval between the catharsis and the administration of the last dose of the salt hardly permits of the latter having taken any part in the production of the former.

Five grammes, therefore, will probably purge. Even a smaller dose may act if it be still more diluted, as in

Experiment II.—Same rabbit as in previous experiment, after a week's interval. Administered *per os* 2 grammes ($2\frac{1}{2}$ per cent. solution), followed in an hour afterwards by another 2 grammes, of same strength of solution. Free fluid purgation during the night.

Four grammes, in this case, well diluted, have produced active catharsis, as is confirmed by the next experiment with another rabbit.

Experiment III.—Rabbit, weighing 1560 grammes. Administered 2 grammes ($2\frac{1}{2}$ per cent. solution), and in an hour afterwards the injection was repeated. Large fluid evacuation during the night.

After an interval of more than a week, this rabbit was used to ascertain if the same weight of sulphate of magnesia ($MgSO_4.7H_2O$), diluted to the same extent, would act equally powerfully.

Experiment IV.—Administered 2 grammes of sulphate of magnesia ($2\frac{1}{2}$ per cent. solution), and repeated the dose in an hour. Active purging during the night.

An equal dose, therefore, of sulphate of magnesia is as purgative, when well diluted, as the same dose of sulphate of soda. It may be well to observe that there was rarely more than one fluid discharge, and that within twelve hours after purgation first occurred the stools in each instance resumed their normal firm consistence. The action of the salt is, therefore, not prolonged.

Throughout these four experiments the rabbits were fed on their usual diet of turnip and brown bread.

The effect of administering the salt in a concentrated form, and to a rabbit which had been more or less deprived of water in its food, was next studied. In Buchheim and Wagner's experiments, a single day's abstention from fluid food was apparently not sufficient to deprive the alimentary canal of its water.[1] Accordingly, in the following experiments, water and turnips were withheld from the rabbits for three or four days previous to the administration of a concentrated solution of the salt, the diet consisting merely of stale wheaten bread, cut from the loaf as required, without being afterwards dried, so that there was still a certain, although small, amount of water in the food. The same diet was continued throughout the experiment. By this means it was hoped to obtain the alimentary canal so free from fluid that, when the concentrated salt was administered, if Buchheim's theory were correct, purgation would not follow.

[1] *Supra*, p. 15.

Experiment V.—Same rabbit as in Experiment I. Fed as described for four days previously. Administered *per os* 5 grammes of sulphate of soda (20 per cent. solution). Next day no purgation; gave 3 grammes (20 per cent. solution). Evacuation of a small quantity of hard fæces in the evening. On the following forenoon a similar small firm stool; injected 5 grammes (20 per cent. solution). No defacation next day. One day afterwards, 80 c.c. of water were twice injected into the stomach, and the rabbit placed on its usual diet. A small amount of purging occurred in the course of the same evening and of the next day.

Experiment VI.—Same rabbit as in Experiment III. Fed on restricted diet during the three previous days. Administered 7 grammes of sulphate of soda (20 per cent. solution) in the forenoon; in the afternoon three or four pellets of hard fæces. Similar evacuation next day. On the third day, still no catharsis.

Experiment VII.—Rabbit of Experiment V. after an interval of over a fortnight. Fed as in that experiment. Administered 8 grammes of sulphate of magnesia (20 per cent. solution). Neither during that day nor the two following was there any evacuation whatever of fæces.

These experiments show most conclusively that, while 4 grammes of a purgative salt will, when freely diluted with water ($2\frac{1}{2}$ per cent. solution), produce their usual effect, a dose twice as large, administered in a concentrated form (20 per cent. solution), and to a rabbit fed for some days previously on a water-restricted diet, is quite incapable of causing purgation.

The alimentary canal of the rabbit is in proportion to the size of the animal much longer than in the cat or dog, in which its relative length more nearly approaches that of the alimentary canal of man. Is the same result obtainable from the cat and the dog as from the rabbit? The succeeding experiments answer the question in the affirmative.

Experiments on Cats.

As with the rabbits, the purgative dose of the salt in a dilute solution and administered under ordinary conditions was first ascertained. The experiments for this purpose were numerous, as I wished to know with perfect certainty as a basis for another series of experiments what dose would, without fail, cause purgation, and yet be not excessive. Very varying results were obtained as to the length of time in which purgation took place, although the salt was given to cats of similar weight and under like conditions. This is probably due more to the degree

of restraint exercised by the animal over defæcation than to a difference in the behaviour of the purgative, the cat from habits of training fearing to defæcate when cooped up in the laboratory. This also applies to dogs which have been accustomed to live in the dwelling-house.

In the following experiments with cats, as well as in those with dogs, no food was given for eighteen to twenty-four hours previously, nor for a few hours after the administration of the salt, in order to ensure that the presence of food in the alimentary tract, or the process of active digestion, would not interfere with the action of the salt. Further, they were for at least a week before the experiment fed on a regular diet, the cats on raw or boiled flesh, and the dogs on bread, and kept under observation, to render the conditions of the various experiments as equal as possible, and to make certain that the stools were of normal consistence. Water was, of course, supplied daily to the animals, unless where the conditions of the experiment required its being withheld.

Experiment VIII.—Grey cat, male, weighing 3·1 kilogrs. Remembering that 4 grammes, well diluted, of sulphate of soda were required to purge a rabbit less than half the weight of this cat, I injected into its stomach, through a catheter, 10 grammes of the salt (5 per cent. solution). After seven hours there was a copious fluid discharge, and purgation continued for three days.

A dose of 10 grammes is apparently too large.

Experiment IX.—White cat, female, weighing 2·63 kilogrs. Administered 3 grammes of the salt (5 per cent. solution). After ten to twelve hours a fairly abundant liquid evacuation.

Experiment X.—Same cat as in last experiment, after an interval of several days. Administered 3 grammes of the salt (10 per cent. solution). Partly watery, but mostly semi-fluid discharge in ten to twelve hours.

Experiment XI.—Black cat, male, of average size, not weighed. Gave 3 grammes of salt (10 per cent. solution). No purgation followed.

Three grammes are, therefore, insufficient to ensure free purgation, although in two out of the three experiments some degree of action followed. I, accordingly, judged that 5 grammes would, in all cases, result in decided catharsis, a supposition confirmed by the next experiments.

Experiment XII.—Grey cat, female, weighing 2·74 kilogrs. Administered 5 grammes of sulphate of soda (5 per cent. solution). Fluid evacuation, tolerably profuse, in about 5 hours.

Experiment XIII.—Black cat, male, weighing 3·45 kilogrs. Administered 5 grammes of salt (10 per cent. solution). Purgation after twelve hours.

Experiment XIV.—Tortoise-shell cat, male, weighing 3·00 kilogrs. Same dose as in previous experiment, but 20 per cent. solution. Purgative effect followed in fifteen or sixteen hours.

Many other experiments were made with the same dose of 5 grammes of sulphate of soda; and if the cat were fed on its usual diet, however concentrated might be the solution of the salt, purgation invariably resulted. But it was observed, as the three last experiments show, that, as a rule, the more dilute the solution, the more quickly was the action produced. Further, it was found that the dose varied extremely little with the size or weight of the animal, as large a dose being required to purge a cat of 2 kilogrs. as one of 4 kilogrs. This I have observed most strikingly in dogs, where the difference in size is much more widely variable; a small terrier requiring nearly as much as a large mastiff perhaps four or five times the weight of the smaller dog.

As to the effect of restriction of the water supply in the diet for two or three days previously, combined with the administration of a concentrated solution of the salt, the succeeding experiments prove that it is much the same with cats as with rabbits.

Experiment XV.—Black cat, same as in Experiment XIII. Fed for the last three days on bread only, very little of which it ate. Administered 5 grammes of sulphate of soda (20 per cent. solution). Fæces, next day, somewhat softer than usual, but still retaining their ordinary cylindrical form, and by no means fluid or even semi-fluid. Never any purgation.

Experiment XVI.—Grey cat, same as in Experiment XII. Fed only on bread for four days previously. Gave 5 grammes of the salt (20 per cent. solution). No evacuation during the next forty-eight hours; perfectly firm when it did appear.

Experiment XVII.—Tortoise-shell cat, same as in Experiment XIV. Water excluded from diet for three days previously. Salt administered in equal dose and concentration to that in last two experiments, and with an exactly similar result.

Experiments on Dogs.

I finally repeated these experiments on dogs in order to obtain all the confirmation possible of the influence exercised by the presence of water in the digestive tract on the action of a saline cathartic. These animals were particularly suitable, as they enabled me at the same time to make some precise analyses of the quantity of the salt recoverable from the urine and the fæces. Some analyses I had made of the urine of the rabbits, but as these were not quite so accurate owing to the difficulty of emptying the bladder at the end of every twenty-four hours or other stated period, and, as in the main, their results agree with those obtained from dogs, I have not thought it worth while to give them. The same objections were open to analyses of the cats' urine, as their urethra is too narrow to admit of the easy introduction of a catheter. On the other hand, a suitable catheter could with the greatest facility be introduced through the wider urethra of the dog, especially of the male, the female not being so convenient for this purpose.

The first experiments were made with the object of ascertaining what dose of the salt was able, under ordinary conditions of dilution and of supply of water in the diet, to produce catharsis; also, how much of the salt was eliminated in the urine, and how much in the fæces. Two dogs only were used, and both of them males. Neither of them, unfortunately, was weighed; the one was rather larger than a sheep dog, and the other was a large-sized terrier. Both tended to be a little constipated, probably from long confinement in the laboratory previous to their being employed for my experiments. Their usual diet was raw flesh and bread, and water *ad libitum;* but for some days previous to an experiment they were fed on bread and water only, in order to obtain fæces comparable in composition with those evacuated whilst they were confined to bread solely, as was necessitated in the experiments requiring absence of water from the food, flesh being then inadmissible on account of its containing too high a percentage of water. As previously mentioned, no food was given on the morning of the experiment; they were fed, however, in the course of the day.

Before commencing the administration of the salt, I esti-

mated in each of the dogs the normal daily quantity of sulphates in the urine and in the fæces.

Experiment XVIII.—The small dog. Fed for the previous week, and during the experiment, on bread and water. At 6.30 P.M., emptied the bladder by means of the catheter, and placed the dog in a zinc cage, so constructed that the urine evacuated was collected in a receiver beneath. Next day, at 6.20 P.M., again catheterised, and the urine obtained added to that in the receiver. The whole measured 527 c.c., and yielded by the careful method of analysis already described 0·281 gramme of sulphuric acid (H_2SO_4), corresponding to 1·0255 grammes of crystalline sulphate of soda ($Na_2SO_4.10H_2O$).

On the third day, catheterised at the same hour as before, the whole urine measured 509 c.c., and yielded 0·276 gramme of H_2SO_4, equivalent to 0·906 gramme of $Na_2SO_4.10H_2O$.

As the fæces were evacuated somewhat irregularly, they were collected for four complete days, commencing four days after the beginning of the bread and water diet. The whole weighed 139·40 grammes. After drying over water-bath, and in air-bath at 110° C., the weight was reduced to 52·165 grammes, corresponding to 62·58 per cent. of water. After complete combustion in a furnace, the ash amounted to 4·42 grammes, and contained 0·3081 gramme of H_2SO_4, equal to 1·0124 grammes of $Na_2SO_4.10H_2O$.

The daily average, therefore, of the sulphuric acid in the fæces of the small dog, reckoned in the form of the sulphate of soda, was 0·2531 gramme, and in the urine $\frac{1·0255+0·906}{2}$ or 0·9657 gramme.

Experiment XIX.—The large dog. Same arrangement of dietary as in foregoing experiment. Emptied bladder at 5.10 P.M. At same hour on following day, bladder again emptied, and urine mixed with that in the receiver; the whole measured 415 c.c., and yielded 0·5481 gramme of H_2SO_4, equivalent to 1·801 grammes of $Na_2SO_4.10H_2O$.

The fæces which were evacuated more regularly than by the small dog were collected for three days; and as I wished to know with accuracy the percentage of water in the freshly-passed stool, each evacuation was weighed as obtained, in order to avoid error from loss by evaporation while standing exposed to the air. The whole fæces for the three days were of the usual firm consistence, and weighed 182·67 grammes, and after drying, 69·78 grammes, and therefore contained 60·7 per cent. of water. The ash amounted to 5·76 grammes, and yielded 0·3194 gramme of H_2SO_4, equivalent to 1·0497 grammes of $Na_2SO_4,10H_2O$.

The daily average of sulphuric acid, estimated as crystalline sulphate of soda, was, accordingly, in the fæces of the large dog, 0·3499 grammes, and in the urine, 1·801 grammes.

These preliminary estimations having been made, I proceeded to ascertain the purgative dose of the sulphate of soda for each of the dogs under ordinary conditions, and to estimate the quantity of the salt recoverable from the urine and the fæces.

Experiment XX.—Small dog. Injected *per os* into its stomach 10 grammes of sulphate of soda (5 per cent. solution). This dose exercised no purgative effect; the fæces evacuated during the three subsequent days were of ordinary consistence.

Ten grammes of the salt were insufficient to produce purgation in the small dog.

Experiment XXI.—Same dog. Administered 15 grammes (5 per cent. solution). In fourteen and a half hours there was a copious discharge of a dark-brown, watery, gruel-like fluid. No purgation, and even no fæces, during the next two days.

Fifteen grammes were apparently a good purgative dose; and this was confirmed by the next experiment, where the salt was given in a more concentrated form.

Experiment XXII.—Same dog. Administered 15 grammes (20 per cent. solution). Purgation in eighteen and a half hours, but stool much less watery and less abundant than in Experiment XXI. As, in that experiment, no fæces were passed during the next two days.

The effect of the concentration of the salt in lengthening the time in which purgation took place, and in lessening the degree of purgation, was as remarkable in the dog as in the cat and rabbit.

That fifteen grammes sufficiently diluted were capable at all times of causing a profuse fluid discharge from this dog was proved by several other experiments, one of which I have selected, accompanied by analyses of the urine and fæces.

Experiment XXIII.—Small dog. Fed, during the experiment, on bread and water, and for three days previously. 9.15 A.M.—Bladder emptied, and 15 grammes of the sulphate of soda (4 per cent. solution) injected *per os* into stomach. The urine was removed by the catheter from the bladder every three hours, in order to prevent its mingling with the fluid fæces which might at any time be discharged. Purgation at 9 P.M., abundant and fluid. Next morning, at 9.15, the bladder was catheterised. No urine was passed during the night, and purgation had not again occurred. The whole urine of the twenty-four hours amounted to 765 c.c., and contained sulphuric acid equivalent to 5·9945 grammes of $Na_2SO_4.10H_2O$, which, after the deduction of the sulphuric acid normally present, shows an excess of 5·028 grammes of the sulphate.

The purgative stool passed the first evening weighed 366·8 grammes, and lost by drying 334·6 grammes, and, therefore, contained 91·05 per cent. of water. By complete combustion the weight was reduced to 5·20 grammes. This yielded sulphuric acid corresponding to 8·485 grammes of $Na_2SO_4.10H_2O$, or an excess of 8·2319 grammes.

Next day, at 9.15 A.M., the urine was again withdrawn from the bladder, and added to what had been passed in the usual way during the previous twenty-four hours. It measured 1090 c.c., and contained sulphuric acid equivalent to 1·4758 grammes of $Na_2SO_4.18H_2O$, or an excess of 0·5101 gramme.

The urine of the third twenty-four hours was obtained in the same manner, and amounted to 612 c.c. It yielded 0·9131 gramme of the sulphate, and, therefore, no excess. The whole of the salt had now been eliminated.

Since the purgative evacuation, no discharge of fæces occurred until between sixty and seventy hours after the administration of the salt. The discharge was soft but solid, and weighed 66·175 grammes, and after drying, 18·9 grammes, thus containing 71·43 per cent. of water. The ash weighed 1·410 grammes, and yielded sulphuric acid equal to 1·046 grammes of sodic sulphate, or an excess of 0·7929, if we regard this small quantity of fæces as not equivalent to more than a single day's evacuation, although it was actually all that was obtained for two days. If we consider it as representing the fæces of two days, then the total excess during that time is reduced to 0·5398 gramme.

A further evacuation of solid fæces occurred eighty-three hours after the administration of the purge. It weighed 28·25 grammes, and was reduced by drying to 10·875 grammes, showing that 61·51 per cent. of water was present. The sulphuric acid was not estimated.

Experiments of the same nature were made on the large dog, and with much the same results.

Experiment XXIV.—Large dog. Fed on bread and water for some days before, and during, the experiment. Administered, at 5.15 P.M., 16 grammes of sulphate of soda (about 7½ per cent. solution). At 11 A.M., on the following day, there was an evacuation mainly of firm fæces, but mixed with a small quantity of watery fluid. The whole weighed 77 grammes, and after drying, 30·240 grammes, and contained, therefore, 60·74 per cent. of water. The ash weighed 3·59 grammes, and yielded of H_2SO_4, calculated as $Na_2SO_4.10H_2O$, 1·202 grammes, or the small excess of 0·852 grammes. As part of the urine was lost it was not examined.

A dose of 16 grammes was evidently too small for so large a dog, and, accordingly, 18 grammes were administered in the next experiment.

Experiment XXV.—Same dog. Fed as in preceding experiment. At 12 noon, emptied the bladder, and injected into the stomach 18 grammes of the salt (6 per cent. solution). The dog licked up a large quantity of water shortly afterwards.

In the course of next forenoon there was evacuated a large quantity of brown perfectly fluid fæces. At noon the bladder was catheterised. The whole twenty-four hours' urine measured 925 c.c., and contained H_2SO_4 equivalent to 9·050 grammes of $Na_2SO_4.10H_2O$, or an excess of 7·249 grammes. The fæces weighed 143·36 grammes, and after drying, 23·954 grammes, and thus contained 83·30 per cent. of water. Of ash there were 5·744 grammes, which yielded H_2SO_4 corresponding to 6·818 grammes of $Na_2SO_4.10H_2O$, or an excess of 6·468 grammes.

On the following day, at 12.10 P.M., the bladder was catheterised and the urine collected as previously. It measured 657 c.c., and gave H_2SO_4 equal to 3·413 grammes of $Na_2SO_4.10H_2O$, or an excess of 1·612 grammes.

On the same day, at 12.20 P.M., the dog evacuated 107·5 grammes of nearly solid fæces, which, when dried, weighed 26·01 grammes, equal to 75·81 per cent. of water. The ash weighed 2·90 grammes, and contained H_2SO_4 equivalent to 1·885 grammes of $Na_2SO_4.10H_2O$, or an excess of 1·535 grammes.

Next day, at 12.15 P.M., the urine was collected in the usual manner. It measured 1060 c.c., and contained of H_2SO_4, estimated as $Na_2SO_4.10H_2O$, 1·7235 grammes, or no excess; on the contrary, the sulphuric acid was slightly under the ascertained normal quantity.

The fæces, evacuated in the course of the forenoon of this day, were, although softer than usual, not so much so as to be pulpy. Their weight was 123·7 grammes, and, when dried, 24·17 grammes; consequently, 80·4 per cent. of water was present. Weight after combustion was 1·95 grammes; and the ash yielded H_2SO_4 equivalent to 0·4968 grammes of $Na_2SO_4.10H_2O$, or the trifling excess of 0·0469 grammes.

Eighteen grammes of sulphate of soda proved, therefore, amply sufficient to purge the large dog. Of course, in all these experiments, a sufficient interval of time, never less than one week, was allowed between them, so that the effects of the one experiment might not interfere with the condition of the animal in the succeeding experiment.

The next experiments are designed to show, what I have already ascertained for rabbits and cats, that, if dogs be fed on a diet tolerably free from water during, and for a day or two before, the administration of the purgative salt, and if, at the same time, the salt be given in a concentrated state, purgation will not ensue.

Experiment XXVI.—Small dog. Fed on bread alone for the two previous days and throughout the experiment; no water. At 5·40 P.M., administered 15 grammes of dry crystalline sulphate of soda, made into large pills or boluses with a little bread and a very few drops of a solution of gum-arabic. The dog's mouth was opened and

the bolus thrust well back into the pharynx, when it was easily swallowed.

As this was one of my earliest experiments I had not yet commenced to withdraw the urine from the bladder: and as micturition did not occur during the whole of the first night and the following day, there was no urine to examine. During the same time there were also no fæces.

On the forenoon of the second day after the administration of the salt, the urine found in the collecting vessel beneath the zinc cage measured 239 c.c., and contained a quantity of H_2SO_4 equivalent to 13·640 grammes of $Na_2SO_4.10H_2O$, or the large excees over the two days of 11·708 grammes.

During the same forenoon, 43·58 grammes of solid dry fæces were passed, which, after dessication, weighed 23·06 grammes, equal to 47·09 per cent. of water. The ash weighed 4·645 grammes, and yielded H_2SO_4 equivalent to 0·3540 grammes of $Na_2SO_4.10H_2O$, or the small excess of 0·1009 grammes.

On the forenoon of the third day, the urine was again collected, and measured 80 c.c. It contained H_2SO_4 corresponding to 1·480 grammes of $Na_2SO_4.10H_2O$, or an excess of 0·5143 grammes.

The fæces passed during the same forenoon weighed 81·2 grammes; although consisting almost wholly of ordinary firm material, a small portion was somewhat softened, but not semi-fluid. The residue after drying amounted to 22·78 grammes, and thus contained 71·95 per cent. of water. The ash weighed 3·941 grammes, and contained 1·792 grammes of H_2SO_4, reckoned as $Na_2SO_4.10H_2O$, or an excess of 1·539 grammes.

Water was now freely added to the dog's diet. Next day, the urine measured 480 c.c., and contained H_2SO_4 corresponding to 3·158 grammes of $Na_2SO_4.10H_2O$, or an excess of 2·192 grammes. There was a moderate quantity of fæces of ordinary consistence, which was not analysed.

Experiment XXVII.—Large dog. Diet of bread during and for one day previous to the experiment; no water. At 5 P.M., emptied the bladder, and administered 18 grammes of crystalline sulphate of soda in the form of boluses as in foregoing experiment.

Next day, at 5 P.M., no fæces; bladder emptied. Whole urine measured 375 c.c., and contained 15·9125 grammes of $Na_2SO_4.10H_2O$, estimated from the H_2SO_4, or an excess of 14·111 grammes.

On the following day, at noon, there was an evacuation of fæces of ordinary firm consistence, which weighed 44·6 grammes, and, after dessication, 20·75 grammes, equivalent to 53·48 per cent. of water. The ash weighed 4·236 grammes, and yielded H_2SO_4 corresponding to 0·3033 grammes of $Na_2SO_4.10H_2O$, or no excess of the salt.

At 5 P.M., on the same day, the bladder was as usual emptied. The urine measured altogether 148 c.c., and, estimated from the H_2SO_4 present, contained 1·5037 grammes of $Na_2SO_4.10H_2O$, or no excess.

During the next, or third, day after the administration of the purge there was no fæcal discharge.

Experiment XXVIII.—Large dog. Simply a repetition of the preceding experiment, the dose of the salt and the conditions of the diet being exactly the same. The urine during the first twenty-four hours amounted to 282 c.c.; and no fæces were evacuated until twenty-seven hours after the administration of the salt. The fæces were of the usual firm consistence.

These experiments with dogs confirm those made with rabbits and cats, and lead to the important result, the demonstration of which has been the principal object of this series of experiments, that a purgative salt, as sulphate of soda, will not produce catharsis if it be given in a state of concentration, and if means be taken to ensure for even a single day previous to the administration of the salt that little or no water is taken with the food. These precautions are intended, as previously explained, to free the alimentary canal as far as possible from fluids.

This result seems to warrant the deduction, that a saline cathartic acts, neither by exciting peristalsis, nor by increasing the intestinal secretions, but merely by uniting with the water in which it is dissolved, and with the fluids which it meets in the alimentary canal, preventing the absorption and preserving the fluidity of the intestinal contents, until the ordinary peristaltic movements have carried them to the rectum. Whether this theory be correct, and with what reservations these experiments must be accepted in its support, I shall fully discuss in the course of the numerous series of experiments which have yet to follow. Meanwhile, it may be affirmed that, by an extension and more strict application of the method of Buchheim, I have succeeded where he failed in establishing proof of the theory he advanced. Two qualities are assumed for purgative salts; one of these, they have already been shown to possess by Graham and others, viz., a low diffusive power; the other quality, a strong affinity for water, is, although generally admitted, extremely doubtful, as I shall afterwards take occasion to point out.

Another result of these experiments, and one of some therapeutical value, is, that the rapidity of action of the salt, and the extent of its action, bear a certain proportion to the degree of its dilution. This is borne out by the experiments in all of the three kinds of animals used, and is perfectly consonant with the theory presently under discussion. The fact is not novel

although in practice often forgotten, and was perfectly well known even to Hippocrates, and apparently applies to vegetable as well as to saline cathartics. We find it expressed in an aphorism of this venerable physician—"Corpora ubi quis purgare voluerit, facile fluentia reddere oportet."[1]

I shall now pass to a consideration of the objections which can be urged against the method I have employed in this series of experiments. It might be said, and with much fairness, that, by a restriction of water in the diet of my animals, I not only freed the alimentary canal from its fluids, but also largely diminished the quantity of water in the blood; so that a concentration of the blood was produced, which did not permit of the usual intestinal secretions being poured out when the glands were stimulated by the presence of the salt. If this be true, it will follow, that, if we feed an animal on a water-restricted diet for some time in order to diminish the fluids within the alimentary canal as far as possible, and, at the time of administration of the salt, inject into the blood a large quantity of water, the condition of concentration being thus overcome, purgation should occur. I made such an experiment with a rabbit, and found that purgation did not ensue, as the following protocol evidences:—

Experiment XXIX.—Rabbit, weighing 1605 grammes, which was freely purged some days before with 4 grammes of sulphate of soda dissolved in a large quantity of water. No water was given for two days previous to this experiment, and the diet consisted of bread alone. At 4.10 P.M. administered *per os* the excessive dose of 8 grammes of crystalline sulphate of soda (20 per cent. solution). 4.25 P.M., commenced injecting into the right jugular vein a warm (35°–40° C.) $\frac{3}{4}$ per cent. solution of chloride of sodium. The solution was allowed to run slowly and continuously into the vein from a burette connected with it, and provided at its lower end with a stopcock for the regulation of the flow. The injection was completed at 7.40 P.M., when 200 c.c. of the solution had been introduced. I feared that, if I had injected the fluid more quickly, it might have been rapidly eliminated by the kidneys, without the salt in the digestive tube having had time to attract sufficient of it to cause purgation. The rabbit micturated twice during the operation, and again immediately after being returned to its box. All the urine passed during the operation was carefully collected with a clean sponge. On being released from the holder, the animal jumped away quite briskly, apparently uninjured by the injection of the large quantity of fluid—nearly twice the total quantity of its blood.

Next day, at 10 A.M., it was found that during the night some fæces

[1] Hippocrates, *Aph.* 9, sect. ii.

had been evacuated, for the most part firm, but mixed with a small quantity of semi-fluid material. There was no purgation, such as might have been expected to follow the administration of a dilute solution of so large a dose of the salt. The urine up to this hour, including that collected yesterday evening, measured 190 c.c., and yielded H_2SO4, corresponding to 4·585 grammes of $Na_2SO4.10H_2O$, or an excess not exceeding 4 grammes.

On the following day, no further evacuation of fæces. Urine measured 33 c.c., and became after cooling thickish and somewhat gelatinous. The diet was still water-free. The urine gave H_2SO_4, equivalent to 1·637 grammes of $Na_2SO4.10H_2O$, or an excess, probably, of about 1·25 grammes.

Although this rabbit was kept under observation for several days more, the fæces never became fluid. The urine, very strangely, became more and more gelatinous; and, on the fifth day from the beginning of the experiment, was so much so as to form a soft gelatine-like jelly, perfectly transparent and of a pale yellow colour. On heating it became fluid, and showed no trace of coagulum. It gave a dense whitish precipitate with tannic acid, which partly dissolved in ammonia, and the filtrate from the solution of the precipitate in ammonia yielded an abundant precipitate with hydrochloric acid. By treating the latter precipitate with oxide of lead, the tannic acid was removed, and there remained after filtration and evaporation of the filtrate a small quantity of a gelatinous material. Whether it was real gelatin or not, the quantity was too small to permit of this being determined by an analysis of its chemical composition. It was probably gelatin. Although water was freely added to the diet, the gelatinous condition of the urine persisted.

The noteworthy result of this experiment is, that the injection of the water into the circulation seems hardly to affect the inaction of the concentrated solution of the salt in the alimentary canal—another proof that the salt is not capable of withdrawing water from the blood through the medium of the intestinal glands, or otherwise, but simply combines with the water it finds already present in the canal. There was certainly a small quantity of semi-fluid fæces, but the amount of purgation is not at all equal to the dose of the purgative administered.

The appearance of gelatine, or a gelatine-like substance, in the urine of this rabbit, although of no importance in connection with the object of the present investigation, is a very unusual and extremely interesting phenomenon, and, so far as I know, a phenomenon hitherto unobserved. It was probably produced by the conditions of the experiment, but how, and by which, or by all, of these conditions I cannot attempt to say.

Vulpian[1] has asserted that a purgative salt acts chiefly by exciting an inflammatory irritation of the alimentary mucous membrane, and consequently creates an exudation such as we observe in a mucous catarrh. Since the irritant action of croton oil is visible even on the skin, we can hardly doubt that the oil also irritates the mucous membrane when in contact with it. But, if the salt and the oil both act in the same manner, an ordinary purgative dose of each should be similarly modified by similar circumstances. If the salt fails to excite secretion, or, at least, produce purgation in an animal deprived of water, equally, should croton oil be without effect, when administered to an animal in the same condition. Is this so?

Experiment XXX.—Small dog. Deprived of water for the previous two days. At 5.10 P.M. administered 5 drops of croton oil in the form of a pill, a dose ascertained under ordinary conditions to produce moderate purgation. A much larger dose is required for the dog than for man. By nine on the following morning, free purgation had occurred.

Croton oil, therefore, can purge where sulphate of soda fails; and the conclusion is evident, that, if the oil acts by causing an inflammatory exudation from the alimentary mucous membrane, the salt does not act in the same manner, and as Vulpian suggests. We are, further, tempted to infer from this experiment that as croton oil is still capable of withdrawing fluid from the blood when the animal has been deprived of its water for a day or two previously, so sulphate of soda, acting under the same condition, should not be prevented from extracting water from the blood, did it ordinarily exercise such an action, whatever be the exact nature of that action. If this inference be legitimate, it lends support to the theory at present being tested. But, it is possible, notwithstanding the result of Experiment XXIX., that, if the salt excite a true secretion and not an inflammatory exudation, a concentrated condition of the blood, arising from a deficiency of water in the diet, may materially diminish the former, while it is unable to any great extent to modify the quantity of the latter.

The experiments hitherto detailed are sufficient to give a *locus standi* to the theory which they were designed to support

[1] Vulpian, *op. cit.*

—that a salt purges in virtue of its combining with the water in the alimentary canal, thus preventing the rapid absorption of the water on account of its own low diffusive power. This was my object when I commenced this investigation. And, indeed, I had hoped to find in this theory a complete explanation of the action of saline purgatives. So far I appear to have succeeded. But it may be well at this stage of the inquiry to frankly admit that the experiments of the various succeeding series have compelled me, by no means unwillingly—for I but sought the truth—to abandon the present view; for what reasons I shall afterwards state.

This admission does not necessarily impair the value of the preceding experiments. They are of themselves of much pharmacological and physiological interest; and the several analyses of the excretions offer some facts of both practical and scientific importance. These we will now consider. For their more convenient comparison, I have arranged them in a tabular form. I need hardly repeat that they were made with the greatest possible care and exactitude, each analysis in almost every instance having been performed twice. We shall first examine the effect of the salt on the urine, and afterwards its effect on the fæces.

The experiments tabulated exhibit a material increase in the quantity of the urine after the administration of the salt in a diluted form, probably in part due to the water given with the salt. As from other experiments, which will afterwards be given, I have observed that the increase is usually best marked on the day following the ingestion of the salt, I may be permitted here to point to Experiment XXIII. as showing this increase very clearly. In the corresponding experiment with the large dog (Experiment XXV.), this rise does not occur on the second day, but on the third, while there is a very large excretion of urine during the first day. This anomaly is probably the result of the unusually large quantity of water which was taken with the salt.

Where the salt has been administered without water to a dog fed on a water-restricted diet, the urine, as might have been expected, is largely diminished in quantity, the effect, in all likelihood, of the mere modification of the diet.

ANALYSIS OF THE URINE AND FÆCES OF THE SMALL DOG.

No. of Experiment.	Diet.	Dose of $Na_2SO_4.10Aq$.	Strength of solution.	Time in which first evacuation occurred.	Day after Administration.	URINE. Quantity.	URINE. Total Weight of H_2SO_4 as $Na_2SO_4.10Aq$.	URINE. Excess of Na_2SO_4 +10Aq.	FÆCES. Weight.	FÆCES. Weight after drying at 110° C.	FÆCES. Percentage of Water.	FÆCES. Weight of Ash.	FÆCES. Total Weight of H_2SO_4 as Na_2SO_4 +10Aq.	FÆCES. Excess of Na_2SO_4 +10Aq.
		grms.				c.c.			grms.					
XVIII.	Bread and water.	...	normal	...	I.	527	1·025	...	...	...	...	...	...	...
	,,	...	...	...	.	509	0·906	...	Aver 34·85	age of 13·41	four 62·58	days. 1·10	0·2531	...
XXIII.	Bread and water.	15	4 %	12 hours.	I.	765	5·9945	5·0280	366·8	32·2	91·05	5·2	8·4850	8·2319
	,,	...	...	...	II.	1090	1·4758	0·5101	66·175	18·9	71·43	1·41 or for	1·046 two days.	0·7929
	,,	...	...	...	III.	612	0·9131	...						0·5398
	,,	...	...	...	IV.	...	...	...	28·25	10·875	61·51	...	...	...
XXVI.	Bread, no water.	15	dry.	...	I.	239	13·640	for two days. 11·708	43·58	23·06	47·09	4·645	0·3540	0·1009
	,,	...	...	45 hours.(?)	II.									
	,,	...	...	...	III.	80	1·480	0·5143	81·20	22·78	71·95	3·941	1·792	1·539
	Water d ded.	...	...	...	IV.	480	3·158	2·192	...	...	...	...	...	...

Analysis of the Urine and Fæces of the Large Dog.

No. of Experiment.	Diet.	Dose of $Na_2SO_4.10Aq.$	Strength of Solution.	Time in which first evacuation occurred.	Day after Administration.	Urine. Quantity.	Urine. Total Weight of H_2SO_4 as $Na_2SO_4 \cdot 10Aq.$	Urine. Excess of Na_2SO_4 +10Aq.	Fæces. Weight.	Fæces. Weight after drying at 110° C.	Fæces. Percentage of Water.	Fæces. Weight of Ash.	Fæces. Total Weight of H_2SO_4 as $Na_2SO_4 \cdot 10Aq.$	Fæces. Excess of Na_2SO_4 +10Aq.
		grms.				c.c.			grms. average	of three	days.			
XIX.	Bread and water.	...	normal	...	I.	415	1·801	...	60·89	23·26	60·70	1·92	0·3499	
XXV.	Bread and water.	18	3°/o(?)	18–20 hrs.	I.	925	9·050	7·249	143·36	23·954	83·30	5·744	6·818	6·468
	,,	...	...	...	II.	657	3·413	1·612	107·5	26·01	75·81	2·90	1·885	1·535
	,,	...	...	...	III.	1060	1·7235	...	123·7	24·17	80·4	1·95	0·4968	0·0469
XXVII.	Bread, no water.	18	dry	...	I.	375	15·9125	14·111	44·6	20·75	53·48	4·236	0·3033	
	,,	...	...	43 hrs.	II.	148	1·5037	...						

Small Dog.

No. of Experiment.	Diet.	Dose of $Na_2SO_4.10Aq.$	Strength of Solution.	Time in which first evacuation occurred.	Day after Administration.	Urine. Quantity.	Urine. Total Weight of H_2SO_4 as $Na_2SO_4 \cdot 10Aq.$	Urine. Excess of Na_2SO_4 +10Aq.	Fæces. Weight.	Fæces. Weight after drying at 110° C.	Fæces. Percentage of Water.	Fæces. Weight of Ash.	Fæces. Total Weight of H_2SO_4 as $Na_2SO_4 \cdot 10Aq.$	Fæces. Excess of Na_2SO_4 +10Aq.
XXXI.	Bread and water.	16	4½°/o	hrs. mins. 10 35	h. m. 10 35	253	5·478	4·503						
XXXII.	Bread, no water.	16	dry	...	h. m. 10 35	138	10·030	9·065						

The salt recovered from the urine, as estimated from the excess of sulphuric acid present, is of more interest. In no case was the whole of the salt administered again obtained from the urine and the fæces. More was always recovered after a dilute than after a concentrated purge. The blood in the latter case seemed to retain the salt for a much longer time than in the former, as was proved in Experiment XXVI., by a considerable excess of the sulphate appearing in the urine after the administration of water, without that the quantity of the urine itself was increased beyond the normal. The time usually required for the elimination of the salt by the kidneys extended over more than twenty-four hours, and the small quantity obtained during the next twenty-four hours renders it highly probable that, under ordinary circumstances, the elimination is completed in from thirty to thirty-six hours from the time of administration.

As regards the amount of the salt recovered from the urine, compared with that obtained from the fæces, from one-half (Experiment XXV.) to nearly one-third (Experiment XXIII.) of the total salt excreted appeared in the urine, when the salt was administered well diluted; and the more pronounced the purgation, the less was the quantity of the salt. On the other hand, when the salt was given in a concentrated form, practically the whole of it passed into the urine. Even did absorption of the salt proceed with equal pace in both classes of experiments, this great difference might be accounted for in this way, that in the experiment with the diluted salt, *e.g.*, Experiment XXIII., a great part of the salt is removed from the alimentary canal with the stool which was evacuated twelve hours after the administration of the purgative, whereas, had purgation not occurred until the end of twenty-four hours, the most of this salt might have been absorbed from the intestines. In other words, the salt does not remain long enough in the alimentary canal to permit of its complete absorption by the blood. In Experiments XXVI. and XXVII., where the salt was given without water, no fæces were passed until the expiry of two complete days, and thus abundance of time was allowed for the disappearance of salt from the canal. The difference can certainly be accounted for in this manner, but the following two experiments will distinctly prove that, apart from the variation in the time allowed for the absorption

of the salt, the more concentrated salt is more rapidly absorbed than the more dilute. This might almost have been taken for granted, were it not that both Aubert[1] and Buchheim[2] expressly state that the extent of dilution of the salt has little or no effect on the rate of its absorption, even when some attempt was made to restrict the water in the diet (Buchheim).

Experiment XXXI.—Small dog. Diet, bread and water. At 9.50 A.M., emptied the bladder, and injected into the stomach 16 grammes of sulphate of soda, dissolved in 350 c.c. of water (about $4\frac{1}{2}$ per cent. solution). The urine was taken from the bladder at intervals of three hours during the remainder of the day. At 8.25 P.M. free liquid purgation occurred. Bladder was immediately catheterised. The whole urine, from 9.50 A.M. until now, measured 253 c.c., and contained H_2SO_4 equivalent to 5·478 grammes of $Na_2SO_4.10H_2O$, or an excess of 4·503 grammes.

Purgation occurred in ten hours thirty-five minutes. In the next experiment, made several days afterwards, exactly the same dose of the salt was administered, but without water, and after the dog had been fed on a water-restricted diet. At the end of the same time, ten hours thirty-five minutes, the urine was collected and analysed.

Experiment XXXII.—Same dog. Fed for two days before on bread only—no water. At 9.50 A.M., bladder emptied; administered 16 grammes of the salt, in the form of large pills, made with a few crumbs of bread. At 8.25 P.M. the bladder was again catheterised. This urine, with that obtained since morning, measured 138·5 c.c., and yielded H_2SO_4, corresponding to 10·030 grammes of $Na_2SO_4.10H_2O$, or an excess of 9·065 grammes. Purgation never occurred.

The salt recovered from the urine in the second experiment was, therefore, twice as much as in the first.

These two experiments decisively prove what the others more or less indicate, that the rapidity of the absorption of the salt is influenced by the degree of concentration of its administration, concurrently with a diminution of the fluidity of the contents of the alimentary canal, and probably also of the fluidity of the blood. The last factor, I am inclined to think from later experiments, is, perhaps, the most important.

We shall now turn to the analysis of the fæces, and it will be found that they present us with some facts of considerable value. The analysis from the large dog are more satisfactory than those

[1] Aubert, *op. cit.* [2] Buchheim, *op. cit.*

from the small dog, as it was of a less constipated habit of body, and, under ordinary conditions, defæcated once a day. The small dog, on the contrary, rarely had stools oftener than once in two or three days, which accounts for the irregularity in the quantity of its fæces. Fortunately, it hardly affects the relative proportions of the constituents of the stools, for the normal excrements of both dogs are remarkably alike in composition, as is more clearly brought out by comparing the percentages of the constituents:—

	Small dog. *Average of four days.*	Large dog. *Average of three days.*
Water, . .	62·58 per cent.	60·70 per cent.
Solids, . .	37·42 „	39·30 „
„ Organic,	34·27 „	36·15 „
„ Inorganic,	3·15 „	3·15 „
H_2SO_4, . .	0·220 „	0·174 „

These analyses were made, as has been previously mentioned, while the dogs were fed on brown bread and water, the diet employed, with or without the water, in all the experiments. It is satisfactory to observe this uniformity of composition, as greater weight can be attached to the variations produced in the fæcal constituents by the action of the purgative. Among these variations, the most notable is naturally that of the water. Beneath 80 per cent. of water the fæces are of plastic consistence; with each additional per cent. of water they become rapidly more liquid. The amount of water, it will be observed, corresponds tolerably with the quantity of the purgative salt in the stools—the more salt, the more water. The salt, in its turn, is less, the longer the interval between its administration and its purgative effect, as, *cæteris paribus*, more of it will have been absorbed from the alimentary tract; so that, within certain limits, the shorter that interval is, the more marked is the purgative effect. This is borne out by a comparison of Experiments XXIII. and XXV., and by other experiments not given. No one will deny its truth when applied to intervals of one or two days; but I have every reason to believe it is equally true for periods of almost as few hours. This is practically stating that the maximum of fluid within the canal occurs shortly after the

ANALYSIS OF THE FÆCES, SHOWING INCREASE OF THE FÆCAL ASH AFTER THE ADMINISTRATION OF A SALINE PURGATIVE (SULPHATE OF SODA).

				I.[1]	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.
				Solids of Fæces.			Ash of Fæces.				Percentage in Solids (III.) of	
	Number of Experiment.	Nature of Experiment.	Day after Administration of Salt.	Total Weight.	Weight of Excess of $Na_2SO_4 \cdot 10 Aq.$	Real Weight.	Total Weight.	Weight of Excess of Na_2SO_4 (water—free).	Real Weight.	Real Weight of Organic Constituents.	Inorganic Constituents.	Organic Constituents.
Large Dog.	XIX. .	Normal.	Average of three days.	23·26	...	23·26	1·92	...	1·92	21·34	8·254	91·746
	XXV. .	Salt with water.	I.	23·954	6·468	17·486	5·744	2·8529	2·891	14·595	16·533	83·467
	,,	...	II.	26·01	1·535	24·475	2·900	0·6769	2·223	22·252	9·083	90·917
	,,	...	III.	24·17	0·046	24·124	1·950	0·0206	1·929	22·195	7·997	92·003
	XXVII. .	Salt without water.	I. and II.	20·75	...	20·75	4·236	...	4·236	16·514	20·414	79·586
	XXIV. .	Salt and water, but only small amount of purgation.		30·240	0·852	29·388	3·590	0·3757	3·214	26·174	10·937	89·063
Small Dog.	XVIII. .	Normal.	Average of four days.	13·41	...	13·41	1·10	...	1·10	12·31	8·202	91·798
	XXIII. .	Salt with water.	I.	32·20	8·2319	23·968	5·20	3·627	1·573	22·395	6·562	93·438
	,,	...	II. and III.	18·90	0·5398	18·360	1·41	0·238	1·172	17·188	6·382	93·618
	XXVI. .	Salt without water.	I. and II.	23·06	0·101	22·959	4·645	0·044	4·601	18·358	20·040	79·960
	,,	...	III.	22·78	1·539	20·241	3·941	0·678	3·263	16·978	16·120	83·880

[1] $I.-II.=III.;\ IV.-V.=VI.;\ III.-VI.=VII.;\ \frac{VI.\times 100}{III.}=VIII.;\ \frac{VII.\times 100}{III.}=IX.$

administration of the salt; and were Buchheim's theory correct, the maximum ought to be coincident with administration.

Of greater interest and practical value is the effect of the purgative on the quantity of the solids of the fæces, especially of the inorganic portion of them. This is best shown by the table on the opposite page, in which I have rectified the modification of the quantity of the solids produced by the presence of the purgative salt. In order to obtain the real weight of the total solids, I have deducted the weight of the estimated excess of crystalline sulphate of soda from the weight of the dried fæces; and to ascertain the real amount of the inorganic solids, the excess of the sulphate, reckoned as water-free, has been subtracted from the weight of the ash, as given in the previous tables. In each case, before drying and burning, the fæces were mixed with 2 grammes of dried carbonate of soda; but that, of course, has been deducted from the weights stated. For reasons already given I am inclined to attach more value to the analyses of the fæces of the large dog.

The most remarkable feature in the table is the considerable increase in the inorganic constituents of the fæces, apart from the purgative salt present. In the case of the large dog, after the administration both of the diluted purge and of the concentrated purge, but notably after the latter, is this increase evident amounting to 1 gramme in the former experiment, and to more than 2 grammes in the latter. The organic matter, meanwhile, remains much as normally, or, if altered, it is diminished, as on the first day of Experiment XXV., where the diminution is probably due to the dog having had no forenoon meal, as always happened on the day of the administration of the salt. In the experiments with the small dog, whilst the same result is very observable, even for three days after the administration of the concentrated salt, yet the diluted salt is not followed by an increase in the proportion of the inorganic to the organic matter, although it causes a small absolute excess of the former. Setting aside this, the sole exceptional result, and for which it may be possible in part to account, as, for example, by the short time the salt remained in the canal, we may reasonably conclude that sulphate of soda and probably other saline purgatives increase the quantity of the inorganic constituents of the fæces, independent

of the salt which they themselves add. The quantity of the organic matter is, on the contrary, little affected. Its increase in Experiment XXIII. is doubtless due to the salt acting on a previously constipated bowel.

What is the composition of this increase of the fæcal ash, and what its source? I regret that, not having observed the increase while making the analyses, I did not examine its composition. It was not due to silica, for that I never found to exceed 5 per cent. of the total ash. It must, therefore, have consisted of salts soluble in water and acid.

The source of the increase of ash could not have been the food, as the same kind of bread was used when the normal ash was calculated as during the purgative experiments. The bread contained 42 per cent. of water, and 1·10 per cent. of ash, and each dog received 500 grammes per diem. The total ash in this quantity would not exceed 5·5 grammes, the greater part of which, consisting of soluble salts, must have been absorbed long before the food reached the rectum; and as defæcation was delayed in those experiments where the ash of the fæces attained its maximum, ample time was allowed for absorption. The source of the ash must, therefore, be the blood, through some form of intestinal secretion. Such a conclusion is inconsistent with Buchheim's theory, but I have already admitted that his theory is insufficient and possibly erroneous. In all probability an intestinal secretion, relatively rich in inorganic but poor in organic matter, is excited both by the diluted and by the concentrated salt. When the latter is administered, the water of the secretion is re-absorbed, whilst its solids, especially the ash, remain within the alimentary canal. To this point I shall return.

The three subsequent series of experiments will show how I was forced to abandon the view with which I commenced this inquiry into the action of saline cathartics. In these will be offered for the first time indisputable proof of the salt exciting secretion within the intestines. The nature of the secretion will likewise be discussed, and notice taken of some remarkable variations in quantity which the salt undergoes in its passage through the alimentary canal.

(*To be continued.*)

Series of Experiments, B.

On the effect of the salt on the intestine, when injected directly into the viscus after the method of Colin and Moreau; with analyses of the fluid, as to the salt it contained, and as to its digestive and other properties.

The method practised by Colin and Moreau, with its modification by Brieger, I have already described.[1] Twenty per cent. or even stronger solutions of the purgative salt, sulphate of soda, or sulphate of magnesia, were used by all the observers who employed this method. In every case there was a considerable flow of fluid into the injected coil, whether the experiment was made on the horse (Colin), the dog (Moreau, Vulpian, and Brieger), the cat (Brunton), or the rabbit and frog (Böttger).

I have repeated these experiments with certain important modifications. It is as yet the only method by which direct proof has been furnished of the salt exciting secretion within the intestines. And it were desirable to know, especially after a consideration of the experiments of Series A. of this investigation, in conjunction with the observations of Thiry, Schiff, and Radziejewski,[2] whether the method employed by Colin and Moreau was reliable. To what extent was the secretion due to the nature of the operation required,—the exposure of the intestine, and its irritation by ligatures, &c.? Perhaps it was caused by the irritant action of the unusually strong solution of the salt injected. Solutions of less strength than 20 per cent., excepting in a single experiment of Brieger's,[3] were not at any time employed; and it is well known that a strong solution of a salt will irritate living tissues, whilst a weaker solution will exercise no such effect. For example, a strong solution of common salt will irritate and inflame even the skin, whilst a 1 or $\frac{3}{4}$ per cent. solution is so bland as to be the fluid commonly used in physiological experiments for the immersion of delicate tissues and organs whose vitality we wish to preserve uninjured

[1] P. 5. [2] Pp. 8, *et seq.* [3] *Infra*, p. 46.

as long as possible. It is certain that the purgative salt never, in ordinary circumstances, reaches the intestines so concentrated as would be implied by a 20 per cent. solution. It is rarely swallowed in a state of such concentration, and in the stomach and intestines it at once mingles with a large quantity of alimentary fluids which quickly dilute it. To settle these and other points is the aim of the present series of experiments. And although I have already thrown aside the theory of purgative action with which I started this investigation, and which I have discussed at length in the preceding experiments, I was still endeavouring, at the time the following experiments were undertaken, to ascertain what of truth or error there might be in this theory which was originally suggested by Buchheim, and brought prominently under my notice by Professor Schmiedeberg. The remembrance of this will sometimes account for the arrangement of my experiments.

In this series of experiments, excepting a few rabbits, cats were always employed. They were more readily procurable than dogs, and in the structure of their alimentary system they more closely resemble man than do rabbits. Moreover, they enabled me to compare my results with those of at least one (Lauder Brunton) of the preceding observers. My method of procedure was as follows :—The animal having been anæsthetised with a mixture of chloroform and ether (1 to 3), which I found to act four or five times as quickly as pure ether, and much more safely than pure chloroform, was attached to a holder placed over a large oblong porcelain tray containing water heated by a bunsen flame. The steam arising from the water in the tray enveloped the trunk of the animal during the operation, and helped to maintain the temperature and moistness of the exposed intestine. The operation consisted in exposing the intestines by a longitudinal incision in the linea alba nearly midway between the processus xiphoideus and the symphysis pubis, and from one to two inches in length. Too short an incision is not advisable, as it is apt to necessitate undue pressure in returning the intestine into the abdomen. Generally not more than a drop of blood was lost in making the incision. The omentum having been carefully drawn up by

introducing the finger or the handle of the scalpel, so much of the intestine was withdrawn from the abdominal cavity as it was desired to operate upon. The part selected of the small intestine was generally situated near to the cœcum. As in each experiment no food had been given since the previous afternoon, the intestines were usually perfectly empty, or contained at most a little gas and a few brownish shreds of incompletely digested food. The diet of the cats, as in the preceding series of experiments, consisted of boiled flesh, along with what of the water in which the meat had been boiled they chose to take. Each animal was fed regularly twice a day for a a week before the experiment, and the healthy condition of its alimentary system was ascertained from the character of its stools. To return to the steps of the operation, a measured portion of the exposed intestine was ligatured off by means of fine caoutchouc tubing, such as is attached to the cannula for draining anasarcous tissues. This form of ligature was sufficiently tight to prevent the passage of fluid through the constricted part of the intestine, and at the same time was sufficiently yielding as not to cut the walls of the intestine, which ordinary thread ligatures are rather apt to do. The ligature was always passed through the mesentery as close as possible to the intestine in order to avoid including the large anastomotic branches of arteries, veins, and lacteals which fringe the mesentery. At the extreme ends of the ligatured coil two short longitudinal incisions were made into its lumen. These were generally followed by a little bleeding. Through the upper of the incisions was introduced a glass cannula connected by an india-rubber tube with a large ball syringe filled with a $\frac{3}{4}$ per cent. solution of chloride of sodium at a temperature of from 35° to 40° C., by means of which the coil was gently but thoroughly washed out as indicated by the purity of the fluid escaping from the lower incision. Due care was of course taken to prevent any of the washings passing into the peritoneal cavity. The small intestine of the cats was found almost invariably to contain several tape worms, and the removal of these with the salt solution sometimes prolonged a little this part of the operation. The object of thus carefully cleansing the intestinal loop was to

ensure that the secretion excited by the afterwards injected purgative would be free from admixture with the biliary and pancreatic secretions and with the products of digestion. In a few experiments where it was desirable to avoid much manipulation of the intestine, and where it was not necessary to ascertain the nature of the secretion, the washing was not practised. A ligature was now placed round the coil, under and close by the upper opening, and the loop was emptied of its salt solution by gentle stripping with the fingers. Another ligature was then applied immediately above the lower incision. The washed empty portion of intestine included between the two last ligatures was next divided into three equal portions by means of other two ligatures, and into the central of the three was injected the solution of the purgative salt. For this purpose a syringe provided with a fine steel cannula was employed, its point being pushed through the wall of the intestine. The viscus was then returned within the abdomen, and the wound in the linea alba was carefully closed with a number of closely set ligatures to prevent the hernial protrusion of any portion of the gut, which was more apt to happen from the not unfrequent occurrence of a little vomiting after the operation—the effect probably of the anæsthetic as well as of the nature of the operation. The animal after being released from the holder was enveloped in a warmed cloth and placed in a basket near the fire. Half-an-hour was generally required for it to regain sufficient consciousness and strength as to be able to sit up; and in half-an-hour more it looked so well—apparently free from pain and even bright and lively—that it would have been difficult to say that the animal had been operated upon. An occasional vomit, and that only in some experiments, was the sole evident indication of its condition. None of the animals were kept so long as to permit of peritonitis with its accompanying pain occurring. Finally, the animal was killed by strangulation, aided by a sharp blow on the head with a mallet.

The method of operation occasionally varied from what I have described, but where any modification was practised it will be recorded in the protocol of the experiment. The time occupied by the whole operation—from the removal of the intestine from

the peritoneal cavity to its replacement—rarely exceeded five minutes. The operation was conducted with the greatest possible expedition in order to avoid the irritation of the intestine resulting from its prolonged exposure.

In arranging my experiments I had some difficulty in deciding what length of intestinal loop I ought to employ. A long loop, otherwise preferable, was objectionable on account of its requiring the exposure and manipulation of a large portion of the abdominal contents. I therefore chose for my first experiments a short loop. Lauder Brunton, probably for a similar reason, employed also a short loop. Most of the other observers, however, made use of loops of considerable length.

Experiment XXXIII.—Cat, female, weighing 1·59 kilogrammes. Operation performed exactly as described above—coil of small intestine washed out with warm $\frac{3}{4}$ per cent. solution of chloride of sodium, emptied and divided by ligatures into three equal portions. Into the central of these was injected 1 c.c. of a 10 per cent. solution of chemically pure crystalline sulphate of soda. The temperature of the solution was about that of the animal (38° C.). The cat was killed *five hours* afterwards, and the abdomen at once opened, and the condition of the intestines noted.

AUTOPSY.—The condition of the loops was as follows :—

Upper control contained 0·1 c.c. of very viscid, colourless, opaque fluid. Lower control contained 0·3 c.c. of a similarly viscid and opaque fluid (slightly reddened).

Injected loop contained 3·45 c.c. of a transparent, colourless fluid, in great part limpid, although mixed with a small quantity of viscid mucus, and with some whitish flocculi. Reaction, alkaline. The reaction of the injected saline solution was, of course, neutral. Caustic potash, with the aid of a little heat, dissolved the viscid flocculent deposit almost completely, which was reprecipitated by acetic acid, and was not soluble to any visible extent in excess of the acid. It, therefore, consisted largely of mucus. The acetic acid filtrate gave no precipitate, but merely a distinct opalescence, with a drop of a solution of ferrocyanide of potassium. A trace of albumen was therefore present. Other reagents for albumen led to the same conclusion.

Microscopically, the flocculent deposit was seen to be composed of mucous corpuscles and mucin, with a number of epithelial cells, and a quantity of granular matter, part of which, from its high refractive power, appeared to be oily in nature. The mucous corpuscles were distinctly nucleated, and had a granular protoplasm.

The mucous membrane of all three loops was perfectly pale, unless in the neighbourhood of the ligatures, where there were very slightly congested zones.

The injected loop measured 6 cm. long, and each of the controls

5 cm. The operated part of the intestine was 15 cm. from the cœcum and 87 cm. from the pylorus. The total length of the small intestine was 122 cm.

A 10 per cent. solution of sulphate of soda appeared, therefore, to be as capable of causing a flow into the intestinal loop in which it had been placed as the 20 per cent. solution used by all previous investigators. An experiment of exactly the same nature was made upon a rabbit.

Experiment XXXIV.—Rabbit, female, weighing 1·47 kilogrammes. Loops prepared as in previous experiment, and 1 c.c. of a 10 per cent. solution of sulphate of soda injected into the middle loop. Killed after *five hours.*

AUTOPSY.—Upper control contained 0·15 c.c. of bloody mucus. Lower control was empty.

Injected loop contained 3·55 c.c. of a colourless, transparent fluid, partly limpid, partly viscid and glairy; no odour; alkaline reaction; specific gravity, 1·0130. It contained a trace of albumen, but no glucose or other material capable of reducing oxide of copper.

Its digestive powers were ascertained. To a portion of it was added a very small piece of fresh fibrin, and the mixture placed in a digesting oven at a temperature of 40° C. After seven hours the fibrin was not dissolved and scarcely diminished in bulk; the fluid did not give the peptone reaction with sulphate of copper and caustic potash. Another portion of the original fluid was mixed with a boiled solution of starch, which was previously ascertained to contain no glucose, as common starch often does, and set aside for a night in a warm place. Next day the mixture gave abundant evidence of the presence of glucose, or rather maltose, according to the researches of Musculus and Von Mering.

The fluid taken from the loop presented the same microscopical characters as that of the previous experiment.

The mucous membrane of the loops was not congested.

The injected loop measured 7½ cm. The seat of the operation was in the upper part of the ileum. The whole length of the small intestine was 258 cm.

The action, then, of a 10 per cent. solution of the salt is much the same in the rabbit as in the cat, and this was confirmed by other experiments.

According to Brieger,[1] who injected a ½ per cent. solution of sulphate of magnesia, as well as a 20 per cent. solution, the weaker solution is absorbed. I have just ascertained that a 10 per cent.

[1] Brieger, *Archiv. f. experim. Patholog. u. Pharmakolog*, Bd. viii. S. 358.

behaves like a 20 per cent. solution, inasmuch as it excites a flow of fluid into the intestine. There must, therefore, exist between the $\frac{1}{2}$ per cent. and the 10 per cent. a strength of solution which will neither excite secretion nor be absorbed. What this strength is the next experiments help to elucidate.

Experiment XXXV.—Cat, male, weighing 1·84 kilogrammes. A set of loops was prepared on both the ileum and the colon. Into the central of each was injected 1 c.c. of a $2\frac{1}{2}$ per cent. solution of sulphate of soda. Killed *three hours* afterwards.

Autopsy.—All the coils were perfectly empty, and the mucous membrane of each was quite pale. The injected ileac loop was 6 cm. long; that of the colon, 2 cm. The ileac loop was 20 cm. from the cœcum and 71 cm. from the pylorus. The injected loop on the colon was 4 cm. from the cœcum.

A $2\frac{1}{2}$ per cent. solution is absorbed whether it be injected into the small intestine or the colon. Will a 5 per cent. solution be likewise absorbed ?

Experiment XXXVI.—Young male cat, weighing 1·41 kilogrammes. An injection of 1 c.c. of a 5 per cent. solution of sulphate of soda was made as in the previous experiment into the large as well as into the small intestine. There were the usual three loops on the former. On the latter there was only one, but with a couple of ligatures at each extremity to shut off the openings by which the loop had been washed out with the chloride of sodium solution. Killed at the end of *five hours.*

Autopsy.—The controls were empty. The injected loop of the small intestine contained 0·3 c.c. of a transparent, colourless, somewhat viscid fluid, with a small quantity of an opaque, yellowish deposit. Reaction, alkaline. In the loop of the colon were found 3·5 c.c. of an alkaline transparent, colourless, extremely viscid fluid, strikingly resembling in consistence and appearance white of egg; it was considerably more viscid than the fluid from the loop of the small intestine; specific gravity, 1·0154. A portion of it was opaque, yellowish-white and flocculent, and looked as if it had formed a layer over the mucous membrane of the loop. This fluid contained no appreciable trace of albumen, although tested with all the common reagents, as nitric acid and ammonia, sulphate of copper and caustic potash, acetic acid and ferrocyanide of potassium. It did not, although appearing to contain a considerable quantity of mucin, give much turbidity with excess of acetic acid. It digested starch with ease.

Microscopically, the fluid from the colon contained throughout a large number of motionless bacteria. The opaque sediment consisted largely of mucous corpuscles, also of epithelial cells of various shapes,

some goblet-shaped, others breaking up or degenerating. There was a large quantity of granular debris, and a few crystals of phosphate of lime and of leucin and tyrosin, which had probably not been removed from the mucous membrane by the washing with the solution of common salt.

The mucous membrane in the loops, both of the small and of the large intestine, was pale and uncongested.

The operated part of the ileum was 5 cm., and that of the colon 3 cm., from the cœcum. Both of the injected loops were 3 cm. long.

The ileac loop was, therefore, half the length of the injected loop in Experiment XXXIII., making the quantity of the salt, in relation to the length of intestine acted on, the same in both cases. Yet at the end of the same time the 5 per cent. solution had diminished to one-third of its original bulk, while the 10 per cent. solution had increased to three and a half times its original quantity.

As the salt had produced a remarkable flow of fluid from the colon as compared with the small quantity obtained from the ileum, it was desirable to know if this difference were constant; for it pointed to the salt in ordinary purgation procuring its fluid in greatest part from the colon.

Experiment XXXVII.—Cat, female, weighing 2·835 kilogrms.

Three loops were as usual formed on the ileum, but instead of the central the two lateral were injected, the one with 1 c.c. of a 5 per cent. solution, the other with 2 c.c. of a $2\frac{1}{2}$ per cent. solution of sulphate of soda, the central loop being preserved in this instance as a control. Both injected loops, therefore, received the same amount of the salt. On the colon were formed two adjacent loops, which were injected with the same quantities of the same solutions as the ileac loops. The cat was killed *two hours* afterwards.

AUTOPSY.—

Ileum—5 per cent. solution had increased to	1·4 c.c.
Colon— ,, ,, ,,	1·2 ,,
Ileum—$2\frac{1}{2}$ per cent. solution had sunk to	1·0 ,,
Colon— ,, ,, ,,	1·2 ,,

The central control on the ileum was quite empty.

The injected loops of the ileum measured 5·7 cm. (5 per cent.) and 5·6 cm. ($2\frac{1}{2}$ per cent.). The two loops of the colon measured each 3 cm. The circumference of the small intestine, obtained by measuring its diameter while distended with fluid under a moderate pressure was 4·2 cm.; of the large intestine, 8·8 cm. The operated part of the ileum was 49 cm. from the cœcum. The total length of the small intestine was 151 cm.

All the fluids were faintly but distinctly alkaline, and all were colourless, transparent, and viscid, those of the colon being the more viscid. All digested starch, and contained very little albumen.

This experiment, in opposition to the previous experiment, seems to indicate that the ileum and colon behave much alike towards equally strong solutions of the sulphate. As the determination of this point is of interest, I shall endeavour to show wherein may lie the reason for the conflicting results of these two experiments. The two essential differences between the conditions of these experiments are to be found in the length of the ileac loop and in the time during which the salt was permitted to act on the intestine. As in both experiments the same quantity of a 5 per cent. solution of the salt was injected, it is obvious that the proportion of ileac mucous membrane to the salt solution must have been greater in the one experiment than in the other. And an alteration in this relation may materially affect the amount of secretion excited by the salt. This remark applies equally to a comparison of this relation in the colon with that in the ileum. Assuming the circumference of the corresponding viscera to be the same in both experiments, the extent of mucous membrane in the injected ileac loop of Experiment XXXVI. was 3 cm. (length) × 4·2 cm. (circumference) = 12 sq. cm.; in the colon it amounted to 3 cm. (length) × 8·8 cm. (circumference) = 26·4 sq. cm. In the next experiment (XXXVII.) the mucous membrane of the ileac loop injected with the 5 per cent. solution measured 5·7 cm. (length) × 4·2 c.m. = 23·8 sq. cm., and of the corresponding loop of the colon, 3 cm. × 8·8 cm. = 26·4 sq. cm. Thus in the latter experiment the two mucous membranes were of nearly equal superficies, in the former that of the ileum was only half that of the colon, and in both experiments the mucous membranes of the colon were of equal extent. In three of the loops, therefore, was the membrane of nearly the same size, while in the fourth it was much smaller. Where those of the ileum and colon are equal (Experiment XXXVII.) the effect of the salt solution is much the same on both. Where they are unequal (Experiment XXXVI.) the smaller the extent of membrane exposed to the action of the salt, the less appears to be the amount of the secretion excited. Such a difference of effect is

what might well be expected. But the next experiment, undertaken with the view of settling this point, seems to indicate otherwise.

The other element of difference in the conditions of the experiments which I am now comparing was that of time. This seems clearly to account for the larger quantity of secretion found at the end of five hours in the colic loop (Experiment XXXVII.) as contrasted with that recovered from the corresponding loop and the ileac loop after the lapse of two hours (Experiment XXXVI.). To what extent it may have influenced the wide difference between the 5 per cent. solutions in the ileac loops, apart from the inequality of their length, will shortly be discussed.

One other point brought out in the last experiment is that the salt dissolved so as to form a 2½ per cent. solution acts on the same length of intestine differently from the same quantity of salt as a 5 per cent. solution. The former solution is gradually absorbed, while the latter increases in bulk, although, from the inequality of their quantities when injected, they do not materially differ in amount at the end of two hours.

Experiment XXXVIII.—Cat, male, weighing 3·63 kilogrammes. Three contiguous loops were formed on the ileum by ligaturing as in previous experiment, two of equal length, but the third or upmost twice as long as each of the others. Into the long loop was injected 1 c.c. of a 10 per cent. solution of sulphate of soda, and into the lower of the short loops a similar quantity of the same solution. The animal was killed *two hours* afterwards.

Autopsy.—Long loop contained 1·44 c.c. of a very viscid fluid; short loop, 3·2 c.c. of a fluid, although viscid, not so much so as that in the long loop. Both fluids were colourless and partly transparent, partly flocculent and opaque. The reaction of both was alkaline.

The long loop measured 11·6 cm. in length, and the short loop, 6·1 cm., and was situated about 6 cm. from the cœcum.

The result of this experiment is not in harmony with the conclusion tentatively expressed, that the greater the extent of mucous membrane exposed to the action of the salt, the less is the secretion, and which was directly inferred from the results of the two preceding experiments. With these opposing results I deemed it necessary to obtain confirmation of the one or the other by another experiment made under conditions slightly

modified from those of the preceding experiment: the time was extended to five hours, and the colon was likewise ligatured and injected.

Experiment XXXIX.—Cat, weighing 2·36 kilogrms.

Five loops were formed on the ileum, two for injection and three for controls, and they were so arranged alternately that an injected coil lay between two controls. Into the longer of the injected loops was placed 1 c.c. of a 10 per cent. solution of sodic sulphate. Into the shorter loop was also injected the same quantity of the salt solution. On the colon was formed a single loop, accompanied by the usual four ligatures, and into it was injected 1 c.c. of the same solution. The cat recovered well from the effects of the anæsthetic, and did not vomit. The intestines contained no tape-worm, so that the washing-out was quickly accomplished, and the operation completed in a few minutes. The cat was killed at the end of *five hours.*

Autopsy.—Condition of ileum:—Long loop contained 0·1 c.c. of an extremely viscid fluid; short loop, 0·88 c.c. of a less viscid, slightly yellowish, gruel-like fluid. Both were alkaline in reaction.

In the loop of the large intestine were 1·88 c.c. of an excessively tough, glairy fluid, almost tougher than white of egg, and mixed with greyish slimy flakes; reaction alkaline.

The longer of the ileac loops measured 14 cm., the shorter 8 cm. The loop on the colon was 5·2 cm. long.

In so far as the length of intestine affects the amount of the secretion, the result is the same as that of the preceding experiment. The larger the loop exposed to the action of a given quantity of the salt solution, the less is the quantity of the secretion, and we may now, therefore, regard this as an established fact.

Here also as in Experiment XXXVII., the fluid in the colon exceeded the quantity of that in the ileum, without that the extent of the mucous surface was less. The fluid was likewise of extreme viscosity, which affords confirmation of the statement met with in some physiological works,[1] that the secretion of the colon contains more mucus than the secretion of the small intestine. The larger amount of the colic than of the ileac fluid is due either to the secreting glands of the large intestine being more susceptible to the action of the salt than those of the small intestine, or to some other changes of which I have not as yet taken cognisance. From a comparison of Experiment XXXVII. with Experiments XXXVI. and XXXVIII., we may conclude

[1] Heidenhain, *Hermann's Hdbuch. der Physiologie*, Bd. v. Th. 1, S. 168.

that if the extent of mucous membrane acted on by the salt be nearly equal in the colon and in the ileum, then, if the action of the salt be interrupted at the end of two hours or so, the quantity of secretion will be found to be much alike in both; but if the salt be allowed to act for five hours, then more fluid will have been secreted in the colon than in the ileum. The explanation is tolerably simple. In both secretion occurs with equal rapidity during the first two hours, or until the salt solution within the intestine is so diluted as no longer to possess excito-secretory power. This point having been reached, absorption begins; but the fluid of the colon containing much more mucin than that of the small intestine is absorbed more slowly, and consequently, at the end of five hours, remains, relatively to the ileac secretion, large in quantity. It is highly probable that mucin is hardly, if at all, absorbed; the water in which it is dissolved alone being removed, a fact to which the viscosity of those fluids which had greatly diminished in quantity point (*e.g.* Experiment XXXIX.), and which is in accordance with what is known of the physiology of digestion.

But we are not done with the apparent contradictions which the results of these experiments present. Much must be allowed for differences in the constitution of the various animals, in the healthy condition of the viscera, and in the effect of more or less manipulation of the exposed gut. If, however, all these conditions be exactly alike in each experiment, then, regarding the body as a mere machine for the time being, the result of each experiment should be in strict accordance with the known and intended alteration of these conditions. And if we have a discordant result where the conditions are generally good, we must search for the explanation in some unheeded difference in the manner or mode of the experiment. These remarks apply forcibly to Experiments XXXIII. and XXXIX., whose results are strikingly at variance. In the former, after the injection of 1 c.c. of a 10 per cent. solution of a sulphate of soda into a certain length of the ileum, by the end of five hours the fluid has increased to 3·5 c.c. In the latter the same quantity of the salt solution in the same time, placed in a loop of nearly equal length in a similar portion of the intestine, has diminished to 0·8 c.c. The result of Experiment XXXIII. was fully con-

firmed by other experiments whose protocols I have not given, and where the ileum alone was ligatured and injected. The sole difference between the conditions of the two experiments lies in the greater number of ligatures applied to the intestines. The more numerous injections made in Experiment XXXIX. can be of little consequence. That this difference is sufficient to account for the opposing results is amply demonstrated by the succeeding experiments, which, at the same time, prove that the result of Experiment XXXIX. was not exceptional. They were designed for the purpose of ascertaining the action of the salt in different portions of the small intestine before I had perceived the explanation of the difference alluded to. A loop on the duodenum, jejunum, and ileum was injected, and associated with each injected loop were five ligatures—the usual two, at each end, binding off the openings through which the loop was washed, and a fifth for the purpose of excluding from the loop the puncture made by the cannula of the syringe; for I had sometimes observed a very slight oozing from the puncture when the loop was largely distended with secretion. There was, therefore, a large number of ligatures. The usual washing out of the intestine was not practised.

Experiment XL.—Cat, female, weighing 2·95 kilogrms.

A loop was formed in the manner described in each of the three divisions of the small intestine—the duodenum, the jejunum, and the ileum. Into each loop was injected 1 c.c. of a 10 per cent. solution of sulphate of soda. Killed at the end of *five hours.*

Autopsy.—The quantity of fluid in the various injected loops was as follows:—

Duodenal	loop	contained	1·1 c.c.
Jejunal	,,	,,	1·05 ,,
Ileac	,,	,,	1·1 ,,

The duodenal fluid was rather limpid, of a yellowish-white colour, and contained a finely divided whitish deposit which was not, as usual, tough and slimy. The jejunal fluid was tinged with a small quantity of blood, and was rather more viscid than the duodenal fluid, and contained some whitish flocculi. The ileac fluid was transparent, colourless, and more viscid than any of the others, with a whitish tough deposit. The reaction was in every case alkaline; and all contained little albumen, and digested starch readily, the duodenal being the most active.

Each loop measured from 6 to 6·5 cm. in length. The duodenal loop was 15 cm. from the pylorus. It was difficult to place it nearer

the stomach without injuring the pancreas, one lobe of which in the cat is closely adherent to the upper part of the duodenum for the greater part of its length. The jejunal loop was midway between those of the duodenum and ileum, the latter being 8 cm. from the cœcum.

In so far as the immediate object of this experiment was concerned, it led to the conclusion that the salt acted equally on all parts of the small intestine.

It at the same time confirmed the result of Experiment XXXIX., and proved that an extensive disturbance of the intestine lessens the amount of fluid in the injected coil. That this could be produced by merely a large number of ligatures, without the prolonged exposure and irritation of the intestine consequent on washing out and injecting several coils, the next experiment is designed to show.

Experiment XLI.—Cat, weighing 2·12 kilogrms.

A loop about the middle of the small intestine was washed out and ligatured and injected with 1 c.c. of a 10 per cent. solution of a sulphate of soda, exactly as in Experiment XXXIII. Immediately afterwards four ligatures were rapidly tied round the cœcal end of the small intestine at a few inches apart from each other, and other four were similarly applied near the pyloric end. The exposure of the intestine was very short. Killed after *five hours.*

AUTOPSY.—The injected loop was 6 cm. in length, and contained 0·1 c.c. of a whitish viscid fluid. The portions of intestine included between the other ligatures were all empty.

In offering an explanation of the difference in the action of the salt on the large and on the small intestines, I have advanced the suggestion that during the first two hours or so after the injection of the salt it excites secretion, and that subsequently, owing to its having become diluted, it begins to be absorbed. Speaking more strictly, during the first period secretion is in excess of absorption, and during the second period absorption is in excess of secretion. For, whenever a watery fluid is injected into the intestine, we must believe that the two processes of absorption and secretion begin simultaneously to act, the excessive activity of the one over that of the other depending on the relation of the absorbability of the fluid to its excito-secretory power. That the salt solution injected, although scarcely increased in bulk at the end of five hours as in the preceding experiments, may, if interrupted at an earlier stage of

its action, show a decided increase, in conformity with my suggestion, is supported by Experiment XXXVI., where even a 5 per cent. solution, at the end of two hours, is increased in quantity in spite of the application of a large number of ligatures. *A priori*, we would expect that a 10 per cent. solution would show an increase. The result of the next experiment, in which all the conditions, except that of time, were exactly the same as in the preceding experiment, realised my expectation.

Experiment XLII.—Cat, female, weighing 1·47 kilogrms.

All the conditions of loop, ligatures and injection, precisely as in the foregoing experiment; but animal killed at the end of *two hours.*

Autopsy.—The injected loop measured 6·5 cm. in length, and contained 3·7 c.c. of a colourless, tolerably viscid fluid, with large white flocculi. Alkaline reaction not strong, but distinct. The rest of the intestine was practically empty. The fluid possessed all the characters usually observed in such fluids—slight opalescence on acidifying and heating, good diastatic power, etc. The mucous membrane of the loop was pale, unless close by the seat of the ligatures, which is the condition ordinarily observed.

Secretion, then, does take place in the early stage of the action of the salt notwithstanding the application of a large number of ligatures. The only explanation that can be offered of the effect of the ligatures on the intestinal secretion is, that by the irritation of their presence they stimulate the absorptive power of the intestine, and, it may be, to a certain extent accelerate secretion, so that, at an earlier stage than without the irritation of ligaturing, absorption is able to counteract and eventually exceed secretion; or that the whole process of the action of the salt is hastened by an equal stimulation of absorption and secretion, the maximum dilution of the fluid being rapidly reached and its absorption quickly succeeding. In any case, there must be stimulation of the absorptive power of the intestine, and as that is accomplished through the action of ligatures placed at a considerable distance from the injected coil, we have every right to assume that there is here the manifestation of reflex stimulation of a set of intestinal nerves whose function it is to control absorption. Thus one more fact is added to demonstrate that absorption is under the influence of the nervous system, as has been satisfactorily proved, for

other portions of the body by the experiments of Brodie, Schiff, and Bernard, but most particularly by those of Goltz.

But, while the probable stimulation of absorption was the reflex effect of a number of ligatures, it was otherwise with the local or direct action of each ligature; for, as will be supported by the succeeding experiments, there is every reason to believe that the ligature, by the irritation and consequent congestion it produces of the immediately adjacent mucous membrane, gives rise to an increased secretion from the portion of the membrane so irritated. Such a zone of congestion, although in many instances extremely narrow, was invariably visible. It could not, however, of itself have been sufficient to cause an accumulation of secretion within a ligatured loop, or the control loops present in nearly all my experiments would not have been so completely empty as they almost without exception were. The central unirritated portion of these loops must have been capable of absorbing the secretion as quickly as it was poured out. The result might naturally be expected to be otherwise when a solution of a purgative salt, or some other body capable of preventing the rapid absorption of the exuded fluid, was present in the loop. The secretion of fluid excited by the salt would then be augmented by that which was due to the mere local effect of the ligatures. To determine the truth of this hypothesis it was only necessary to perform some experiments in which the relative interference of the ligature secretion with the salt secretion should be reduced to a minimum by greatly extending the length of loop ligatured and equally increasing the amount of salt injected, whereby the salt secretion would be correspondingly increased without altering the amount of the ligature secretion. In some of the experiments already detailed I had observed the influence of different lengths of intestine on a given quantity of salt solution. Now, without altering the relation of the length of the intestine to the amount of the salt, I proposed to ascertain the effect of equally increasing both. The amount of secretion resulting from the injection of 1 c.c. of a 10 per cent. solution of the salt into a loop about 6 cm. long I had already observed, and it will be remembered that where it was unaccompanied by an excessive number of ligatures the secretion was abundant (Experiment XXXIII.

and others). Would the effect be proportionately the same if, say, the length of the coil was increased to 54 or 60 cm., and the amount of salt solution to 9 or 10 c.c., each being multiplied by 9 or 10? These experiments I undertook the more willingly as they offered the further prospect of a more complete and satisfactory examination of the secreted fluid than hitherto I had obtained owing to the small amount of the secretion.

As in none of the previous experiments had I been able to detect the escape of fluid from the injected loop into the adjacent controls, it appeared that the ligatures were in all cases applied sufficiently tightly to prevent such an escape, and to warrant the abandonment of the use of the two additional ligatures required for the controls.

The experiments were conducted in other respects in the manner previously described, the loop being well washed out with a warm $\frac{3}{4}$ per cent. solution of common salt. Five ligatures were in each case necessary, unless where otherwise stated—two for the first demarcation of the loop, two to exclude the openings by which the loop had been washed, and one to shut off the puncture made at its one extremity by the injection-cannula.

Experiment XLIII.—Cat, male, weighing 3·51 kilogrammes. After the ligatures had been applied the loop was found to measure about 50 cm. long, and, accordingly, I injected 9 c.c. of a 10 per cent. solution of sodic sulphate. Killed at the end of *five hours.*

Autopsy.—The fluid in the loop measured 5·6 c.c., and was colourless, opaque, and tolerably viscid, and alkaline in reaction. The opacity was caused by minute whitish flocculi. A few fragments of tape-worm, which the previous washing had failed to dislodge, were also present. That the ligatures were not so loosely applied as to permit the escape of some of the secretion from the loop was ascertained by attempting before opening the loop to press with considerable force some of the fluid through the ligatured ends of the loop, but not a drop flowed out. This precaution was used in every subsequent experiment. The injected loop was 51 cm. long, and was 12 cm. distant from the colon, and 63 cm. from the stomach.

The fluid after standing for a night became extremely tough, and altogether rather like a bronchitic sputum without the air-bubbles. Microscopically, the deposit consisted of a large number of nucleated, distinctly granular corpuscles, many of which were aggregated into mulberry-like groups; most of the corpuscles were globular, but a few were elongated, and almost perceptibly tailed. There was also a quantity of fine granular material resembling the debris of degenerated cells; some faintly fibrillar homogeneous matter was probably

mucin. A few granular columnar epithelial cells with large nuclei were also visible, as well as a very few nearly empty so-called chalice cells. There were no red corpuscles. I have not attempted to distinguish between mucous and lymph corpuscles, as physiologists are not generally agreed in what essential features the one differs from the other. According to the usual distinction most of the corpuscles appeared to be mucous.

The fluid contained a trace of albumen, and gave a distinct precipitate with acetic acid, insoluble in excess, indicating the presence of mucin. The whole of the fluid was carefully collected from the microscopic slide, test-tube, and loop, the last of which was infused several times in water, and the infusion added to the fluid, and the mixture analysed to ascertain the quantity of sulphates present. For this purpose it was evaporated to dryness, burnt with a little dried carbonate of soda, and the ash dissolved in hydrochloric acid and water, and the sulphuric acid estimated in the filtrate by the usual method. The quantity of sulphuric acid recovered, estimated as $Na_2SO_4.10H_2O$, was 0·041 gramme, or only a fraction of what had been injected.

The result of this experiment was remarkable. The salt solution, instead of increasing in amount, as might have been expected from a knowledge of the action of the salt as exhibited in Experiment XXXIII., had diminished.

Was this diminution due to causes similar to those which lessened the fluid in the experiments with a large number of ligatures? Had the exposure of the large loop of intestine during the time occupied in washing it irritated it much in the same manner as the excessive number of ligatures, so that its absorbing or secreting activity was affected? Another experiment, in which all irritation was as much as possible avoided, appeared therefore desirable.

Experiment XLIV.—Cat, male, weighing 3·40 kilogrammes. Small intestine was exposed, and about 50 cm. quickly measured and ligatured. The loop was quite collapsed and empty, and was neither stripped nor washed out. Into it were injected 10 c.c. of a 10 per cent. solution of sulphate of soda, heated to 35° C., and, as before, the puncture was ligatured off. Altogether three ligatures were applied, and the time of exposure of the intestine did not exceed two minutes. Killed *five hours* afterwards.

Autopsy.—The loop contained 6 c.c. of a somewhat viscid, colourless fluid, transparent where unmixed with yellowish-white, extremely tough flakes, which constituted the larger part of the liquid. Reaction, alkaline. The exact length of the loop as measured after death was 52 cm. The mucous membrane was distinctly paler than in the

remainder of the small intestine, which was collapsed and empty in its whole extent. The total length of the small intestine was 153 cm., and the loop was 7 cm. from the cœcum. The stomach contained 2·5 c.c. of a frothy yellowish fluid, acid in reaction. In the colon was a quantity of firm fæces, but no fluid.

The fluid obtained from the injected loop along with several infusions of the latter yielded 0·101 gramme of $Na_2SO4.10H_2O$, reckoned from the sulphuric acid.

This experiment in its result was an exact confirmation of Experiment XLIII., both showing that in a sufficiently long loop a 10 per cent. solution of sulphate of soda is diminished rather than increased during a five hours' stay in the intestine. It were, however, possible that in the earlier part of the action of the salt there was an actual increase of the secretion, which had diluted the salt sufficiently to permit of its absorption before the expiry of five hours, as had already been observed with regard to injected loops influenced by the presence of many ligatures. The next experiment shows that there was no such increase of the fluid during the earlier part of the action of the salt.

Experiment XLV.—Cat, female, weighing 2·29 kilogrammes. Injected into a loop of the small intestine, washed out, and ligatured as in Experiment XLIII., 9 c.c. of a 10 per cent. solution of sulphate of soda. The cat vomited a very little about one hour and a quarter after the operation. Killed in *two hours.*

Autopsy.—On exposing the intestines *immediately* after death, the following appearances were noted, and, although specially mentioned here, were common to all the experiments of the same kind. Peristalsis was rather less active in the injected than in the uninjected part of the intestine. The former was distinctly paler than the latter, and its blood-vessels were less distended and less prominent. No part of the intestine contracted very readily on being lightly stimulated, and still less so the injected loop. After removal from the abdomen by detachment from the mesentery, the excitability of the muscular walls of the injected loop was little, if at all, increased. On the other hand, the remainder of the intestine was sensible to very slight simulation, contracting firmly and often permanently along a much greater part of its length than that irritated.

The injected loop, which measured 44 cm., contained 9·9 c.c. of a partly limpid, partly viscid fluid, colourless and transparent, unless where mixed with some faintly yellowish-white flocculi. Reaction, alkaline.

Microscopically, the deposit presented the same characters as in Experiment XLIII., but contained rather more mucous corpuscles.

A portion of the fluid boiled did not show any visible coagulum. Treated with excess of acetic acid the unboiled fluid deposited a moderate quantity of mucin, the filtrate from which, mixed with a drop of a solution of ferrocyanide of potassium, became very faintly opalescent, indicating the presence of a mere trace of albumen. This was confirmed by other delicate proteid reactions.

The fluid digested starch readily, and inverted cane-sugar. Collecting carefully all the various portions of the fluid and adding the infusion of the loop, and allowing for the sulphate of copper used in testing for albumen and sugar, the whole mixture yielded 0·322 grammes of $Na_2SO4.10H_2O$, estimated from the sulphuric acid recovered.

These three experiments, presenting results in perfect concord, more than prove what I expected, that the increase of the salt solution witnessed in a short intestinal loop is in large part due to the local irritation of the ligatures. For when a much longer loop was injected, with the ligatures so widely apart that the secretion they excited could exert but little appreciable influence on the large mass of injected fluid, then a 10 per cent. solution of sulphate of soda was found not to have increased in volume, whether examined two hours or five hours after injection. Had it increased to the same extent as in Experiment XXXIII., where 1 c.c. became 3·45 c.c., the 9 c.c. ought to have swelled to 30 c.c.

Had these last experiments been made previous to those which form the earlier part of this series, I would doubtless have been satisfied with the support and proof they offered of the theory I sought to establish in the first series of experiments—that the salt does not excite secretion, but merely prevents the absorption of the fluid in which it is dissolved. And even taking into consideration all the experiments of this series I have as yet recorded, they do not present much in opposition to this theory but what might be roughly explained by the conditions of the experiments. But in attempting a precise explanation of many of the phenomena observed, I have assumed that the salt excites intestinal secretion; and this is borne out, even in those cases where the injected fluid undergoes no increase, by an examination of the chemical characters and digestive properties of the fluid. If the bulk of the fluid is not increased, it is because absorption has proceeded as rapidly as secretion. The small quantity of the salt recovered from the injected loop (Experi-

ments XLIII., XLIV., and XLV.), the viscidity of the fluid, and its action on starch and cane-sugar, all prove that the salt solution has undergone considerable changes, which can only be accounted for by a free secretion, obscured in certain cases by an equally free absorption.

Proceeding to make a practical application of the results of these experiments, are we to believe they fairly represent what occurs when an ordinary dose of the purgative salt is administered by the mouth? Am I right in assuming that the salt is diluted to at least a 10 per cent. solution before it passes into the intestine; and does the salt solution, diluted to that strength by the alimentary fluids, undergo no increase in the canal, although exciting secretion; or is the proportion of the salt solution to the length of intestine acted on too small in my experiments to represent what happens when the salt reaches the intestine after administration in the usual manner; and will an alteration of this proportion affect the amount of the fluid within the canal? Further, if the salt can reach the intestine in a more concentrated solution than 10 per cent., may the action of the concentrated salt be different from that of the diluted salt? All other observers employed a 20 per cent. solution for injection into the intestine, and obtained in many cases a very large increase of fluid.

In answer to the first of these questions, as to the strength of the salt solution when it passes into the intestines from the stomach, and as to the proportion of it to the length of the intestines acted on, I think we have every right to assume that the salt is very rarely stronger than 10 per cent. when it passes through the pylorus. A dose of the salt, say an ounce, is generally taken, dissolved in almost a tumblerful or 10 ounces of water, including that which is customarily drank immediately afterwards; and even if it be taken more concentrated, it is very likely to meet with sufficient fluid in the stomach to dilute it to at least a 10 per cent. solution. So there can be no objection to the strength of the solution I have employed. The proportion of the salt solution injected to the length of intestine acted on is not, however, so free from fault. And an alteration in this proportion may very materially affect the bulk of the fluid, as Experiments XXXVIII. and XXXIX. have proved; although

in these the coils were so short that the difference observed may be largely attributable to the effect of the ligatures. There a given quantity of a 10 per cent. solution of the salt showed much the larger increase in the longer of two loops, which is equivalent to stating that if the loops be made of equal length, and more of the salt solution be injected into the one than into the other, the secreted fluid will be relatively much larger in the former than in the latter. It is probable, therefore, that had I injected more than 9 or 10 c.c. into a loop 50 to 60 c.c., as in the last three experiments, the solution, instead of showing no increase, might have been considerably augmented. But it is yet to be decided whether the proportion of the salt solution to the length of intestine did not represent what actually occurs when the salt is administered *per os.* In the cat, the animal used in the foregoing experiments, the small intestine varies, as I have frequently ascertained by measurement, from 110 or 120 to 170 cm. Now, as the salt solution will pass through the pylorus comparatively slowly, the first portion of the salt will almost have reached the cœcum before the last portion has left the stomach, so that the 5 grammes of salt, the purgative dose for a cat, will be distributed over the whole length of the small intestine. There will thus be 1 gramme for every 22 to 34 cm. of intestine. But, if it happens that a portion of the salt has passed into the colon before the last of it has left the stomach, then this proportion may be diminished to 1 gramme for every 40 or even 60 cm. In my experiments the proportion was 1 to 60, and this in some cases might represent what takes place. But in all likelihood the proportion is greater—1 to 30, or so. The proportion I used was arbitrarily chosen, and without regard to the point now under discussion. If the proportion be increased to 1 to 30 (or 2 to 60), will the effect of the salt solution exhibit the same difference in the large loops as it did in the short loops of Exp. XXXVIII. and XXXIX.? For this is the important point. Experiment answers in the affirmative.

Experiment XLVI.—Cat, male, weighing 2·86 kilograms. Loop of small intestine washed out and ligatured in the usual manner, and injected with 20 c.c. of a 10 per cent. solution of sulphate of soda. After death the loop was found to measure 54 cm. long. The animal was killed in *five hours.*

Autopsy.—The loop contained 34 c.c. of a fluid possessing much the same characters as the fluids previously obtained,—colourless, somewhat viscid, containing only a trace of albumen, and capable of digesting starch and cane-sugar.

In Series D. of my experiments, where I had occasion to inject the whole length of the small intestine, ligatured at both its extremities, but excluding the pancreatic and bile ducts, with 5 grammes of the salt in the form of a 10 per cent. solution, I found that the 50 c.c. injected generally increased within a short time to about 100 c.c. There is, therefore, hardly any doubt that, if the proportion of the salt solution to the length of the intestinal loop be greater than 1 to 60, there will be an increase in the bulk of the fluid, and this is probably what occurs when the salt is given by the mouth. So that in this point of proportion many of my experiments are open to objection, without, however, greatly impairing their interest and physiological value.

We have yet to discuss the effect of the salt reaching the intestine in a possibly more concentrated solution than 10 per cent. This I have already stated as being highly improbable. But, apart from its probability, the investigation of this point will be of interest as forming the link between my experiments and the experiments of Colin, Moreau, Vulpian, Lauder Brunton, and the others who injected a 20 per cent. solution of the purgative salt into the intestine. Will a given weight of the salt injected into a given length of intestine affect differently the resultant quantity of fluid according as the salt solution is concentrated or dilute? Although this has already been answered in the affirmative, in so far as short loops are concerned, by Experiment XXXVII., is was desirable to investigate the matter further.

Experiment XLVII.—Cat, male, weighing 2·03 kilogrms. Injected into a loop of the small intestine (which was after death ascertained to measure 52 cm., and was situated 9 cm. from the cœcum, and 67 cm. from the pylorus), 4½ c.c. of a 20 per cent. solution of sulphate of soda, containing, therefore, as much salt as 9 c.c. of a 10 per cent. solution, the quantity used in the preceding experiments. The loop was previously washed out as usual. A little vomiting occurred during the recovery of the animal from the anæsthetic condition. Killed at the end of *three hours.* During this interval it evacuated a small

quantity of firm fæces, the only occasion on which I have observed this occurring in the whole of these experiments.

AUTOPSY.—The loop was tolerably distended with 36 c.c. of a colourless, opalescent, somewhat viscid fluid, mixed with white mucous flakes. Reaction, alkaline; 0·318 c.c. of the pharmacopœial standard solution of oxalic acid [1] was required to neutralise 10 c.c. of it. The acid solution actually used was ten times more dilute than the pharmacopœial.

Examined for albumen, the fluid gave a slight opacity with excess of acetic acid and a drop or two of ferrocyanide of potassium. Compared with an equal quantity of pure saliva in a similar-sized test-tube, and treated with the same reagents, the opalescence of the former was a shade more distinct than that of the latter. I made this comparison in order to ascertain by a simple method whether the quantity of albumen present in the intestinal fluid exceeds that found in other alimentary secretions. A large quantity of albumen would have given support to Vulpian's view,[2] that the secretion is of an inflammatory character. Heated with sulphate of copper and caustic potash, a very faint violet was produced, which was not deeper than that given by saliva with these reagents. No blackening with acetate of lead, and therefore no sulphides. (It has been stated by some authors [3] that the purgative sulphates are partly decomposed in the canal, forming sulphides, which by irritating the intestinal mucous membrane excite secretion). Excess of chlorine water added to the intestinal fluid did not, even after several hours, produce any change of colour, as it is stated to do with pancreatic juice.[4]

In order to ascertain quantitatively the diastatic power of the fluid, 5 c.c. of it were mixed with 100 c.c. of a 1 per cent. solution of pure starch. Both fluids were previously tested for glucose or maltose, and found to contain none. The mixture was placed in an oven at a temperature of about 50° C., and tested at intervals of ten minutes for maltose. Fehling's solution was employed for this purpose, and within thirty minutes the first evidence of the presence of maltose was obtained. The mixture was then digested for forty-eight hours, by which time the action of the ferment might be supposed to be exhausted. It now abundantly reduced Fehling, and 10·5 c.c. of it decolorised 20 c.c. of Pavy's modification [5] of Fehling's solution, equivalent to ·0135 grammes of maltose. The 5 c.c. of the original intestinal fluid therefore contained sufficient ferment to form 0·128 gramme of maltose from starch.

The inversive power of the fluid was similarly measured. 5 c.c. of the intestinal fluid were mixed with 1 gramme of cane-sugar dissolved in 100 c.c. of water, and placed in the digesting oven. Tested fre-

[1] 100 c.c. of the standard solution of oxalic acid of the British Pharmacopœia contain 6·3 grms. of the crystalline acid.

[2] *Supra*, page 7.

[3] Buchheim, Arzneimittellehre, 3 Auflage, S. 133.

[4] Hoppe-Seyler's *Physiologische Chemie*, S. 258.

[5] A mixture of Fehling's solution with a large quantity of strong ammonia.

quently for six hours afterwards it gave no indication of inversion having occurred. Next day, or nearly twenty hours after mixture, it reduced Fehling at once. Allowed to stand for another day, 12·3 c.c. sufficed to decolorise 20 c.c. of Pavy's solution, so that the whole fluid contained 0·081 grms. of maltose; and this, therefore, represents the inversive power of 5 c.c. of the intestinal fluid.

Half of the original fluid, along with half of the infusion of the loop, yielded 0·311 grammes of $Na_2SO_4 \cdot 10H_2O$ (as reckoned from the sulphuric acid), or for the whole fluid 0·622 grammes.

The mucous membrane of the injected loop was perfectly pale, and exhibited not the slightest signs of congestion in any part of its length unless in the immediate neighbourhood of the ligatures.

As this experiment differed so remarkably from the preceding three in the large amount of secretion excited by the salt, it was thought desirable to obtain confirmation of its correctness.

Experiment XLVIII.—Cat, female, weighing 1·36 kilogrms., very lean. Injected 4½ c.c. of a 20 per cent. solution of sulphate of soda into a loop of the small intestine, which was ascertained after death to be 60 cm. long and 7 cm. from the cœcum. The intestine was not washed out, but the same number of ligatures was applied as if it had been, in order to render the conditions similar to those of preceding experiments. Immediately after recovering from anæsthesia it vomited a little, and for some time kept mewing rather loudly as if suffering pain. This was the first, and, indeed, the only occasion, on which I observed a cat giving evidence of suffering pain after the operation practised, as the animal usually rested quietly and placidly. Killed at the end of *five hours.*

Austpoy.—The injected loop contained 8 c.c. of a yellowish-white viscid fluid, mixed with a large quantity of flaky mucus; reaction, alkaline. A very slight hæmorrhage had taken place into the peritoneal cavity from the neighbourhood of one of the ligatures. The control loops formed by the additional ligatures were empty; and the ligatures at the ends of the injected loop were found to be sufficiently tight to prevent any escape of fluid.

This experiment, therefore, presented a widely different result from the preceding experiment. The saline solution, as in experiments where a 10 per cent. solution was employed, had scarcely increased in bulk, and certainly did not exhibit the remarkable increase observed in Experiment XLVII. The result of the one or of the other experiment must be incorrect, owing to bad conditions. These are most apparent in Experiment XLVIII., where the animal seemed to suffer pain, and it is possible that reflex inhibition of secretion or stimulation of absorption

may have been induced by the circumstance which occasioned the pain—perhaps, the inclusion of a mesenteric nerve in the intestinal ligatures, or of a cutaneous nerve in the abdominal sutures. I therefore inferred that Experiment XLVII. presented the more reliable result. But this required confirmation, and necessitated the experiment which follows.

Experiment XLIX.—Cat, male, weighing 2·21 kilogrammes. Injected into a loop of the ileum, without previous washing-out, $4\frac{1}{2}$ c.c. of a 20 per cent. solution of sulphate of soda. The usual number of ligatures were placed round the intestine. Killed after *five hours.*

AUTOPSY.—The loop contained 54 c.c. of nearly colourless fluid, mixed with a very little brownish shreddy material, probably a residue of the food, also with a quantity of whitish flocculi. Reaction was alkaline, 10 c.c., requiring 0·444 c.c. of the standard solution of oxalic acid for neutralisation.

The fluid became distinctly opaque on the addition of acetic acid and ferrocyanide of potassium; and compared with saliva, by placing it in an equal-sized tube and diluting it until a similar degree of opacity was reached, I believed it to contain about twice as much albumen as that secretion. The excess of albumen was easily accounted for by the presence of a little incompletely digested food in the injected loop. Other reagents for albumen gave the same result. 5 c.c. of it mixed with 100 c.c. of a 1 per cent. solution of pure starch gave the first indication of the presence of maltose in about fifteen minutes, and, after standing for forty-eight hours, yielded 0·4890 grammes of maltose. Other 5 c.c. mixed with 100 c.c. of a 1 per cent. solution of cane-sugar digested it slowly, and gave at the end of forty-eight hours 0·093 gramme of invert sugar. Half of the original fluid with half of the infusion of the loop yielded 0·412 grammes of $Na_2SO4.10H_2O$, or, for the whole fluid, 0·824 grammes.

The injected-loop measured 53 cm. long, and was emptied before injection by gentle stripping, washing out having been omitted, as I wished to complete the operation as quickly as possible in order to avoid prolonged exposure and irritation of the intestine.

The mucous membrane of the loop was quite pale, and was covered with a layer of viscid mucus mixed with epithelial debris.

The result of this experiment is in harmony with that of Experiment XLVII. In both there was a very decided increase of fluid after the injection of a 20 per cent. solution of the salt, in the proportion of 1 gramme of the salt to 60 cm. of intestine, or the same as used in Experiments XLIII., XLIV., and XLV.; and we may safely conclude that the result of Experiment XLVIII. was exceptional.

Before proceeding to compare the effects of a dilute and a

concentrated solution of the salt as brought out in these experiments, the digestive capabilities of the intestinal fluids obtained will be alluded to. The diastatic power of the secretion was in no case great. The more energetic action of the fluid of Experiment XLIX. was, doubtless, due to the presence of a small quantity of pancreatic juice, from the loop not having been washed out. The action of the secretion on cane-sugar was still less marked. The exact extent of the action is in each case recorded in the protocol. Some additional experiments were made to ascertain in how far the secretion was able to digest albumen and fat. Placed in a digesting oven with a small piece of fibrin, the fluid gave no evidence of peptones, except in the case of Experiment XLIX., and then only a trace, even after several hours, although the fibrin was generally in part dissolved. The secretion also failed to digest or emulsify fats in the form of pure acid-free cod liver oil, neither when first mixed with it, nor after standing for nearly twelve hours.

Passing now to a comparison of Experiments XLIV., XLV., and XLVI. with XLVII. and XLIX., we are confronted with the surprising fact that a given quantity of sulphate of soda, injected into a certain length of intestine, will, if dissolved as a 10 per cent. solution, cause little or no alteration in the volume of fluid within the intestinal loop; but, if the same amount of the salt be injected in the form of a 20 per cent. solution, or twice as concentrated as the other, and into the same length of intestine, it will provoke a large flow of secretion, far beyond what is necessary to bring the salt to the same state of dilution as in the former case, and where we might have expected its increase to be arrested. This difference of effect between the strong and weak solutions is not in accordance with what was observed in Series A. of experiments to follow their introduction by the mouth. There it was remarked that the more concentrated the salt, the less powerful, or at least the more delayed, was its action. It is not difficult to understand how this may be. For, excluding these experiments where water was withheld from the diet of the animals for some days previously, a concentrated solution of the salt would, when administered *per os*, become quickly diluted in the stomach or upper part of the intestine, either by the fluids present or

by the secretion excited, or by both, and passing into the general length of the intestine, would then merely exert the action of a weaker solution under this disadvantage, that the blood, having already in the upper part of the alimentary canal supplied it with some of its fluid, and thus become more concentrated, would less freely permit of secretion in the intestine generally, and thus delay purgation. It is otherwise when the concentrated salt is kept for some time in contact with the intestine in a ligatured loop. The solution, although diluted by secretion, is acting on a mucous membrane, altered by the application of an originally concentrated salt. What the nature of this alteration is, cannot be easily determined. It is not a strong irritation and inflammatory condition of the intestine, or the mucous membrane would have been congested, which it on no occasion was; and the secretion ought to have contained excess of albumen, which it never did. The concentrated salt evidently produces some more subtle and less obvious change, whereby the secreting power of the intestine is increased or its absorptive power is diminished; for either the one or the other, or a combination of them, will suffice to increase the fluid. Disregarding any impression which the salt may make upon the secretory nervous mechanism of the intestine, and which may be maintained for some time after the cause has disappeared or the salt become diluted, it is probable that the concentrated salt affects the absorptive more than the secretory power of the mucous membrane. For we cannot well conceive of the salt producing in the secretory cells of the Lieberkühnian follicles any change, other than inflammatory irritation, which would not pass away with the dilution of the salt. On the other hand, there are several facts which give countenance to a supposed diminution of the absorptive power of the membrane. Absorption, without doubt, is for the most part effected through the agency of the cylindrical epithelium covering the villi of the intestine; and any injury to this must impede absorption. Now, in microscopical sections of the mucous membrane of the various injected loops, I have observed that chalice or goblet-shaped cells were unusually abundant where the solution injected was 20 per cent. The chalice cells were evidently formed from the cylindrical cells by the action of the salt; and we may

assume, without being at variance with the most recent physiological knowledge, that the former cells have a much lower absorptive power than the latter. A 10 per cent. solution did not produce nearly so many chalice cells.

That the absorptive power of the mucous membrane of the intestine was lessened by a strong solution of the salt, was further supported by the fact, that after the action of such a solution, much more of the salt was recovered from the contents of the loop than after the action of a weaker solution. The salt recovered in the last six experiments clearly shows this. A thick, viscid, layer of mucus was generally observed coating the surface of the mucous membrane after the action of the concentrated salt, and this also may have offered a hindrance to absorption.

An examination of these various points has led me, therefore, to conclude that the difference between the action of a 20 per cent. solution of sulphate of soda and of a 10 per cent. is due more to impeded absorption than to accelerated secretion. There is yet some experimental evidence to adduce in favour of this view, and which I shall now present.

Moreau[1] recently communicated to the Académie de Médecine the results of a number of experiments which went to prove that sulphate of soda or sulphate of magnesia when injected into the intestine is not absorbed. This fact he urged as of great importance in showing the fallacy of the belief, entertained by Liebig, Rabuteau, and others, that osmosis plays a part, if not the sole part, in the production of secretion by the salt. It seems hardly necessary to combat Moreau's statement with further experiment than is offered in Series A. of this paper, where a large proportion of the salt was in several instances recovered from the urine. More than this I should not have done, had I not, previous to having read Moreau's communication, made two experiments by a method like his, for the purpose of ascertaining whether absorption took place more rapidly from a loop containing a 20 per cent. solution of the salt than from one containing a 10 per cent. solution. Moreau injected a 20 per cent. solution of the salt into the ligatured intestinal loop of a dog, and a few minutes afterwards injected into the same loop a solution

[1] Moreau, *Bulletin de l'académie de médecine*, 2me série, t. viii. 1879, p. 357; *ibid.* p. 367.

of ferrocyanide of potassium. In no instance, and his experiments were numerous, could he discover the ferrocyanide in the urine with the usual reagents—perchloride of iron or sulphate of copper. He did not take the precaution of concentrating the urine by evaporation before testing, which would have rendered his analysis more satisfactory. Absorption, as I have already observed, is doubtless impeded, but is not in abeyance; and the ferrocyanide, passing very slowly into the blood and reaching the urine in still more diminished amount, may not have been present in that secretion in sufficient quantity to yield a perceptible colour with the reagents. Moreau draws no distinction between the action of a concentrated salt and a dilute salt, and evidently believes that the action of a 20 per cent. solution injected directly into the intestine represents what happens when it is given by the mouth. Even apart from the experiments of Series A., I did not doubt the absorption of a 10 per cent. solution, if for no other reason than that so little of the injected salt could be recovered from the loop. Where a 20 per cent. solution was injected, the salt unrecovered was so small that it might readily have been imbibed by the tissues of the intestine without actually passing into the circulation, so that I had reason to doubt its absorption, conceiving that the mucous membrane might be so altered by the strong solution as to be incapable of absorbing. This led to the two following experiments being devised. They happily, at the same time, offer a complete refutation of Moreau's *prima facie* unlikely conclusions. My method chanced to be similar to Moreau's; but, instead of the ferrocyanide, I used strychnia, a poison which, if absorbed by the blood, will very quickly manifest its effects without its being necessary to detect it chemically.

Falck[1] states that 0·75 milligrm. per kilogrm. of the animal's weight is the smallest lethal dose for a cat. I injected rather more than double that proportion in each of the following experiments:—

Experiment L.—Cat, male, weighing 2·75 kilogrms. Exposed the small intestine and injected into a loop of it, ligatured as usual, 10 c.c. of a 20 per cent. solution of sulphate of soda. The intestine was returned within the abdomen, and the edges of the parietal incision

[1] Falck, *Rossbach u. Nothnagel's Arzneimittellehre*, 1878, S. 699.

held together, so as to prevent exposure of the gut for the next fifteen minutes, when it was again withdrawn,—the salt, meanwhile, having had sufficient time to produce its action on the mucous membrane of the loop. 1 c.c. of a solution of strychnia, containing 5·16 milligrms. of the alkaloid, was then injected into the centre of the same loop, the cannula of the syringe being first directed towards one extremity, and afterwards towards the other extremity of the loop, so as to ensure mixture of the strychnia with the salt solution.

In twenty-one minutes after the injection of the strychnia, the first symptoms of its action became apparent in the form of slight twitchings of individual muscles. The animal was released from the holder immediately after the completion of the operation, and was tolerably conscious when placed on the floor, so that the anæsthetic did not retard the advent of the toxic symptoms. In nine minutes more there were well-marked tetanic spasms of the whole body, throwing it into the opisthotonic position. These continued with very short remissions until the respiratory muscles became involved and breathing was arrested. Three minutes later, or thirty-nine minutes after the injection of the alkaloid, the heart's action ceased. During this period so much of the strychnia must have been absorbed as was necessary to cause death. According to Falck's statement of the lethal dose, this quantity must have corresponded to about one-half of what was injected.

Autopsy.—The loop was 52 cm. long, 12 cm. from the cœcum, and contained 36 c.c. of a yellowish-white viscid fluid. Half of the fluid, with half of the infusion of the loop, yielded 0·691 gramme of $Na_2SO_4.10H_2O$, and therefore from the whole fluid there was recovered 1·382 grammes out of 2 grammes injected.

Although the fluid was not well suited for ascertaining the diastatic power of the secretion owing to the intestine not having been previously washed out, yet 5 c.c. of it were mixed with 100 c.c. of a 1 per cent. solution of starch, and digested in an oven. Seven hours afterwards maltose first made its appearance. For the sake of comparison 52 cm. of the uninjected portion of the small intestine, washed and cut into very small shreds, were infused in 36 c.c. of distilled water. After macerating for one day, 5 c.c. of the infusion were mixed with 100 c.c. of a 1 per cent. solution of starch. Maltose appeared in from five to six hours, but not distinctly until near the end of the eighth hour. Both the secretion and the infusion were without action on cane-sugar. This is to be attributed to certain conditions which I hope to incorporate in another paper. It is interesting to have observed that the diastatic power of the secreted fluid was not stronger than a corresponding infusion of a fresh portion of the intestine.

The mucous membrane of the injected loop was, as in previous experiments, perfectly pale.

Experiment LI.—Cat, male, weighing 2·77 kilogrms—of the same sex, and nearly of the same weight and size as that used in the preceding experiment. The operation was in all respects the same as the other with the important exception that 20 c.c. of a 10 per cent.

solution of sulphate of soda were injected instead of 10 c.c. of a 20 per cent. solution—therefore, the same amount of salt but more concentrated. Fifteen minutes later the same quantity of the strychnia solution was injected as in the last experiment. Within two minutes some slight general twitchings of the muscles were observable. In six minutes more the animal gradually assumed the opisthotonic position, and two minutes afterwards there was a severe general tetanic spasm. The spasm was renewed within a minute, and continued without relaxation until the animal died, thirteen minutes and a half after the injection of the strychnia.

Autopsy.—In the injected loop, which measured 56 cm. in length, and was situated 8 cm. from the cœcum, were 26 c.c. of a colourless limpid fluid mixed with a small quantity of shreddy undigested remnants of food. As 21 c.c. had been injected, including the 1 c.c. of the strychnia solution, there was an increase of 5 c.c., which is to be explained by the amount of the 10 per cent. solution to the length of intestine injected exceeding the proportion in which I have found no increase to take place.

These two experiments conclusively prove, if such proof were necessary, that, in opposition to the statement of Moreau, the small intestine retains its power of absorption even when a 20 per cent. solution of a purgative salt has been injected. They also show, what previous experiments have led me to believe, that the absorptive power of the intestine is less injured by a weak solution of the salt than by a strong solution.

It were possible, as I have hinted, that some viscid or other character of the fluid secreted under the stimulus of the concentrated salt might in part, if not wholly, account for the slow absorption of the secretion and its consequent accumulation within the intestine. For the secretion obtained by the action of the concentrated salt was always more viscid than when the diluted salt was employed; and a layer of thick tough mucus was generally observed lining the mucous membrane of the loop into which the former had been injected. To settle this point, yet another experiment was made, in which a 20 per cent. solution of the salt was removed from the intestine after it had been allowed to act for an hour. The injected loop was then carefully washed out, and a portion of it injected with a fresh but weak saline solution, the remainder receiving nothing. For the sake of comparison, an unused part of the intestine was injected with the same weak saline solution. The result gave further confirmation of the conclusion to which the previous

experiments led, that the absorptive power of the intestine was largely impaired by the action of the concentrated salt.

Experiment LII.—Cat, female, weighing 2·05 kilograms. Small intestine exposed, and 64 cm. measured off and ligatured, and washed out with a warm $\frac{3}{4}$ per cent. solution of chloride of sodium. The openings formed for the purpose of washing were ligatured off, and the loop thus prepared was divided into two unequal parts by another ligature, the one part being, as nearly as possible, twice the length of the other. Into the longer were injected 10 c.c. of a 20 per cent. solution of sulphate of soda, but nothing into the shorter. The intestine was returned within the abdomen, and the parietal wound was closed with a clamp for an hour, during which the animal was kept lightly anæsthetised. At the end of the hour the intestine was again exposed, and the injected loop was observed to be well distended with fluid, which was now removed by a small incision in one extremity of the loop. The fluid measured 26 c.c., and was clear, colourless, and distinctly viscid, becoming much more viscid after standing for an hour or two; it contained a large amount of opaque, viscid, flaky material. The uninjected portion of the loop was perfectly empty. The injected loop was next carefully washed out with a warm 1 per cent. solution of sulphate of soda, and emptied, and the opening was ligatured off, and the loop divided into two equal parts by another ligature. There were, therefore, altogether three loops of nearly equal length on the intestine. Into one of these nothing had been as yet injected, whilst the other had suffered from the action of a 20 per cent. solution of sodic sulphate. Into the first of these, and into one of the other two, were now injected $7\frac{1}{2}$ c.c. of a 1 per cent. solution of the salt. The third was not interfered with. The cat was killed one hour afterwards.

Autopsy.—The twice injected loop contained 7·8 c.c. of a colourless fluid, mixed with some white viscid flocculi, and was alkaline in reaction. The other, but only once, injected loop contained 1 c.c. of a viscid fluid. The third loop, forming the half of the longer loop previously injected with the strong solution of the salt, and afterwards emptied, contained not a drop of fluid.

From this experiment we learn that after the removal of a strong solution of sulphate of soda from a loop into which an hour previously it had been injected, fluid no longer accumulates within the loop. But if a very weak solution of the salt be injected into such a loop it will not disappear as it does from a fresh loop. The latter fact shows that the absorptive power of the mucous membrane has been impaired by the action of the strong solution of the salt; the former points to the viscid absorption-hindering character of the secretion excited by the salt as being a factor in the increase of the contents of the

loop. For, if instead of a weak solution of the salt, had the fluid secreted by the concentrated salt been allowed to remain in the loop, previous experiments teach us that the fluid would have continued to increase; and this was not due to the excessive excito-secretory power of the salt present, as by the time of its removal from the loop it was so diluted (10 c.c. to 26 c.c.) that its strength was even less than 10 per cent., a strength which we know in the proportion injected does not cause accumulation of fluid within the loop in which it is placed.

A careful examination was made of the digestive properties of the 26 c.c. of intestinal fluid obtained at the end of the first stage of the last experiment. This was the more exactly done, as at the time I was making a number of experiments to ascertain the comparative digestive powers of several animal fluids and secretions, in order to have some idea of the relative importance of the digestive power of the intestinal juice. As in testing its diastatic activity I formerly observed within what time maltose first made its appearance when the intestinal fluid was mixed with a 1 per cent. solution of starch, I adopted the same method in the present examination, altering, however, the proportion of the fluid to the starch solution, from 5 to 100 to 5 to 10. For I had observed that the greater the amount of the starch solution, and, especially, the stronger the solution, the later appeared the maltose; and working with weak diastatic fluids, as intestinal juice, if the starch solution were strong enough, say 5 to 10 per cent., maltose never appeared, or at least was not detectable by means of Fehling's solution. This may account for the variety of opinion existing as to the diastatic power of the intestinal juice. 5 c.c. of the intestinal secretion of the last experiment were, therefore, mixed with 10 c.c. of a 1 per cent. solution of starch, and placed in a digesting oven. Within half an hour maltose appeared, and by the end of five hours the mixture ceased to colour iodine either blue or red, showing that both starch and erythrodextrin, the intermediate product in the digestion of starch, had completely disappeared.

Other 5 c.c. were mixed with 10 c.c. of a 1 per cent. solution of cane-sugar. In one hour there was a trace of invert-sugar, which after some hours became more, but never very, distinct.

To yet other 5 c.c. were added 0·5 gramme of fresh fibrin. In

two hours there was no perceptible change. Four hours later it was completely disintegrated, and for the most part dissolved. The fluid gave a very feeble peptone reaction, but a considerable deposit with the albumen precipitants, so that, although the fibrin had been dissolved, not much of it had been peptonised or truly digested. The alkali of the intestinal secretion had, no doubt, dissolved the albumen, forming with it an alkali-albuminate.

The digestive action of the secretion on fat was finally tested. A few cubic centimetres of it were shaken up with a few drops of acid-free cod liver oil, but failed to emulsify them. Mixed, however, with slightly rancid or acid oil, it produced some degree of emulsion. This was evidently dependent on the alkalinity of the secretion due, probably, to the presence of carbonate of soda. A dilute solution of this salt formed a well-marked emulsion with the rancid, but none with the pure, oil. A fat-splitting ferment is generally believed to be present in the pancreatic juice, although Roberts[1] in his recent Lumleian lectures throws a doubt on its existence. And since the intestinal secretion failed to produce an immediate emulsification of fats, I endeavoured to ascertain, by digesting it for some time in an oven with oil, if it also contained this peculiar ferment. For this purpose some of the secretion was mixed with a few drops of pure acid-free cod liver oil. The mixture was slightly alkaline, and did not form an emulsion on shaking. After three hours the mixture was almost neutral, and formed a slight but distinct emulsion on shaking. A small quantity of the fatty acids had therefore been set free, which, becoming saponified by the alkali of the secretion, slightly emulsified the oil. If more of the fatty acids had been disengaged than there was free alkali to unite with, then the addition of a drop or two of the carbonate of soda should have converted them into soap and increased the degree of the emulsion. Carbonate of soda, although added to a portion of the mixture, did not, however, render the emulsion more distinct. Again placed in the digesting oven, and examined after other three hours, the mixture on being well agitated did not show a better emulsion than previously; but, although neutral litmus paper was not visibly reddened, the emulsion became much more

[1] Roberts, *Digestive Ferments*, 1880.

pronounced on the addition of a drop of a solution of carbonate of soda. The oil had, therefore, been partly decomposed by the intestinal fluid, but very slowly. The method I have employed for detecting the presence of free fatty acids by adding an alkaline carbonate, and observing the degree of emulsion produced on shaking, seems to me a much simpler and more efficient method than testing the acidity of the fluid as is commonly done. It is extremely difficult to obtain evidence of an acid reaction when there is only a trace of free fatty acids, and this difficulty has been the cause of many contradictory statements as to the fat-splitting power of even the pancreatic juice.

I have throughout this series of experiments regarded the action of the salt as purely local, and not appreciably involving any part of the nervous system outside of the intestinal wall. Professor H. C. Wood's experiments, of which I have already taken notice in the historical part of this paper,[1] appear to indicate that section of the vagi is capable of preventing purgative action by inhibiting secretion. He administered arsenic and croton oil to several cats with divided vagi without inducing purgation, but it is not stated in the short report of his experiments, which I have had the opportunity of perusing, whether he examined the intestines after the administration of the purge, and found them empty. The failure of these substances to purge might have been due as much to paralysed or even irregular peristaltic movements as to inhibited secretion. To decide whether the action of a saline purgative was similarly affected by division of the vagi the following experiment was made:—

Experiment LIII.—Cat, female, weighing 2·25 kilogrms. Cut the vagi in the neck, carefully avoiding injury of the sympathetics, which in the cervical part of their course are closely united to the vagi. Immediately afterwards the abdomen was opened, and 10 c.c. of a 20 per cent. solution of sulphate of soda were injected into a collapsed and empty loop of the small intestine, which was previously ligatured. Killed after the lapse of *two hours*.

Autopsy.—The loop measured 63 cm. long, and contained 32 c.c. of a colourless, slightly opaque, viscid fluid, with the usual alkaline reaction.

Division of the vagi had not, therefore, in this experiment interfered with the excito-secretory power of a strong solution of

[1] *Supra*, p. 12.

a saline purgative. In how far it might have affected the peristalsis of the intestines, the experiment fails to show. But the deduction is important, that the salt can purge, in so far as it excites secretion, independently of the vagi, and that Wood's experiments do not prevent me from endeavouring, as I have done, to find in the intestine itself, and in the nature of the fluid injected and secreted, a sufficient explanation of the phenomena hitherto observed. Moreover, the results of Wood's experiments stand in contradiction to those obtained by John Reid,[1] who claimed to have observed that arsenic increased the intestinal secretion in animals with divided vagi.

With this experiment I conclude Series B., and in order to admit of a ready comparison of the results of the various experiments I subjoin them in a tabular form. Cats were employed for all the experiments, with the exception of XXXIV., in which a rabbit was used.

The main object of this series of experiments was to ascertain whether, in contradiction to the theory previously expressed, a purgative salt excites a flow of secretion from the intestine. A careful consideration of all the experiments leads but to one conclusion—that a purgative salt (sulphate of soda), whatever be its amount, or its strength of solution, invariably excites more or less secretion; and that, depending on the relative activity of absorption and secretion which processes proceed simultaneously in the intestine, the bulk of the injected saline solution increases, diminishes, or remains constant in amount.

The detailed results obtained are many of them striking, and I briefly recapitulate them:—(1) A 20 per cent. solution of the salt always excites a profuse secretion: (2) a 10 per cent. solution also increases in bulk, if injected in sufficient quantity; (3) but if in limited quantity (10 c.c. to 60 cm. of intestine) it does not increase; (4) whereas a 20 per cent. solution, containing the same quantity of the salt, and injected into the same length of intestine increases very largely in volume: (5) nevertheless, secretion is active in (3), as ascertained from the change in the characters of the fluid, but is balanced by absorption; (6) and while secretion may be more or less stimulated in (4), absorption is greatly impeded but not in abeyance, as Moreau would have us

[1] John Reid, *Physiolog. Anatom. and Pathological Researches,* 1848, p. 241.

believe; for the injected salt has diminished in quantity, and strychnia can still pass from the loop into the circulation: (7) after removal of the secreted fluid in (1) or (4), no more fluid accumulates within the loop; (8) but, although there is no

Number of Experiment.	Portion of Intestine Injected.	Length of Loop.	Quantity of Solution of Sulphate of Soda Injected.	Strength of Salt Solution.	Duration of Action.	Quantity of Fluid recovered from Loop.	Quantity of $Na_2SO_4.10H_2O$ recovered from Fluid.
		cm.	c.c.	per cent.		c.c.	grms.
XXXIII.	Ileum.	6	1	10	5 hours	3·45	...
XXXIV.	Ileum.	7·5	1	10	5 ,,	3·55	...
XXXV.	Ileum.	6	1	$2\frac{1}{2}$	3 ,,	0	...
	Colon.	2	1	$2\frac{1}{2}$	3 ,,	0	...
XXXVI.	Ileum.	3	1	5	5 ,,	0·3	...
	Colon.	3	1	5	5 ,,	3·5	...
XXXVII.	Ileum.	5·7	1	5	2 ,,	1·4	...
	Colon.	5·6	2	$2\frac{1}{2}$	2 ,,	1·0	...
	Colon.	3	1	5	2 ,,	1·2	...
	Ileum.	3	2	$2\frac{1}{2}$	2 ,,	1·2	...
XXXVIII.	Ileum.	6·1	1	10	2 ,,	3·2	...
	Ileum.	11·6	1	10	2 ,,	1·4	...
XXXIX.	Ileum.	8	1	10	5 ,,	0·8	...
	Ileum.	14	1	10	5 ,,	0·1	...
	Colon.	5·2	1	10	5 ,,	1·8	...
XL.	Duodenum.	6·1	1	10	5 ,,	1·1	...
	Jejunum.	6·5	1	10	5 ,,	1·05	...
	Ileum.	6·2	1	10	5 ,,	1·1	...
XLI.[1]	Ileum.	6	1	10	5 ,,	0·1	...
XLII.[1]	Ileum.	6·5	1	10	2 ,,	3·7	..
XLIII.	Ileum.	51	9	10	5 ,,	5·6	0·041
XLIV.	Ileum.	52	10	10	5 ,,	6	0·101
XLV.	Ileum.	54	9	10	2 ,,	9·9	0·232
XLVI.	Ileum.	54	20	10	5 ,,	34	...
XLVII.	Ileum.	52	$4\frac{1}{2}$	20	3 ,,	36	0·622
XLVIII.	Ileum.	60	$4\frac{1}{2}$	20	5 ,,	8	...
XLIX.	Ileum.	53	$4\frac{1}{2}$	20	5 ,,	54	0·824
L.[2]	Ileum.	52	10	20	54 mins.	36	1·382
LI.[3]	Ileum.	56	20	10	28 ,,	26	...
LII.[4]	Ileum.	...	...	...	...	...	...
LIII.[5]	Ileum.	63	10	20	2 hours	32	...

[1] Excessive number of ligatures.
[2] Death in 39 minutes after injection of strychnia into loop.
[3] Death in $13\frac{1}{2}$ minutes after injection of strychnia into loop.
[4] *Vide* protocol.
[5] Vagi divided.

further accumulation of fluid, the relation of the secretive to the absorptive power of the loop is altered, the latter being weaker than the former, or the former relatively stronger than the latter, as compared with their ratio previous to the injection of the salt: (9) the local effect of a ligature applied to the

intestine is to excite secretion from the mucous membrane in its immediate vicinity, and therefore add to the bulk of the saline solution; (10) the reflex effect of a ligature, as exercised through the nervous system, is, on the contrary, to diminish the quantity of the secreted fluid, probably by stimulating and accelerating absorption : (11) division of the vagi does not affect the quantity or nature of the secretion : (12) all parts of the small intestine yield an equal amount of secretion when acted upon by the salt; (13) and the large intestine behaves in a similar manner towards the salt, excepting that, partly from the greater viscosity of its secretion, and partly from the nature of its mucous membrane, absorption proceeds with greater slowness than in the small intestine: (14) the secreted fluid does not contain more than a trace of albumen, and not more than is present in ordinary saliva, and cannot, therefore, be an inflammatory exudation, as Vulpian suggests: (15) on the other hand, it always contains much mucin, especially when obtained by the action of a 20 per cent. solution of the salt: (16) the fluid possesses, although in small degree, all the digestive properties attributed by most physiologists to the succus entericus—converting starch into maltose, inverting cane-sugar, splitting up fat, and dissolving, if not peptonising, albumen: (17) the mucous membrane is without exception pale, rather than congested, after the action of the salt—another fact opposing Vulpian's view: (18) and, finally, no increase in the vigour of the peristaltic movements of the injected loop of the intestine was ever visible.

Some of these results are of purely physiological interest, and help but little to solve the nature of the action of a dose of a saline purgative when administered in the usual manner. They, however, serve to determine the value of a method which has been much employed in recent years to ascertain the action of medicines and particularly of purgatives on the intestines, and, as yet, the only method by which it has been shown that a purgative salt excites secretion from the intestinal wall. They indicate how comparatively trivial alterations in the conditions of the method may greatly affect the issue of the experiment, and they will thus tend to render more accurate and trustworthy the work of succeeding investigators. Yet this method of Colin and Moreau is open to serious objection on account of

the necessarily great disturbance of the abdominal viscera occasioned by their exposure; and while, as I have already stated, it clearly leads to the conclusion that the purgative salt excites secretion within the intestine, proof must still be furnished of the truth of this occurrence by such methods as will be free from the disturbance of an abdominal operation. The next two series of experiments supply this want; and until these have been presented no attempt will be made to explain and reconcile the opposing results of the experiments of this and the preceding series.

Series of Experiments, C.

The effect of saline purgation on the concentration of the blood.

The first series of experiments tended to show that the salt when administered without water, or with insufficient water, was not capable of purging; and the conclusion naturally was that the salt did not excite secretion, or draw fluid from the blood. But, as in order to free the alimentary canal from fluids the animal received no water with its food for one or more days previous to the administration of the salt, it was possible that in addition to the canal being freed from its water, the blood had become considerably concentrated from the deprivation of its water-supply, while the kidneys continued to secrete almost as abundantly as usual. The concentration of the blood thus effected might have resisted the abstraction of fluid by the salt, and have constituted the principal if not the sole cause of the absence of purgation when the salt was administered with little or no water. I have already suggested this explanation, and I shall offer the proof of its probability in the course of the following experiments.

One other fact of primary importance is brought out by these experiments. Whatever action a diluted solution of the salt may have in exciting intestinal scretion, the strongest evidence will be furnished of a concentrated solution abstracting a large amount of fluid from the blood.

In order to ascertain the degree of concentration of the blood, the number of corpuscles in a given quantity of it was from time to time counted according to the method introduced by Vierordt, and afterwards improved by Malassez and Hayem. I reckoned an

increase in the number of the corpuscles as equivalent to a loss of serum, and a diminution as indicating dilution of the blood.

The relation of the number of the blood-corpuscles to the quantity of the serum is greatly altered, as is well known, in many diseases, notably in anæmia. These alterations are believed to be almost entirely due to the diminution or increase of the total number of the blood-corpuscles in the body, the serum undergoing no alteration in quantity. There are, however, physiological variations of daily occurrence, which are to be attributed to no change in the number of the corpuscles, but to the diminution or increase of the liquor sanguinis, and are mostly the effect of diet and digestion. Thus, after a meal, Sörensen, Dupérié, Buntzen, and others have shown that the blood becomes more concentrated from a large part of its water passing out in the alimentary secretions—the gastric, pancreatic, and intestinal juices, and the bile. The concentration will be less, or not at all, discernible, according as little or much fluid is taken with the food; for that being absorbed will take the place of the fluid which has been poured out in the secretions. When the food after digestion begins to be absorbed and pass into the circulation, the concentration of the blood is relieved.

If the food can by its withdrawal of water from the blood make this ascertainable through the relative increase of the corpuscles in the blood, it is to be expected that a purgative salt, if it excites secretion, should have its action similarly registered by a concentration of the blood. But, as when much fluid is consumed with the food, no concentration of the blood occurs, so it may be anticipated that only a strong solution of the purgative salt will thus affect the blood, a weak solution permitting of an absorption which equals in amount the secretion.

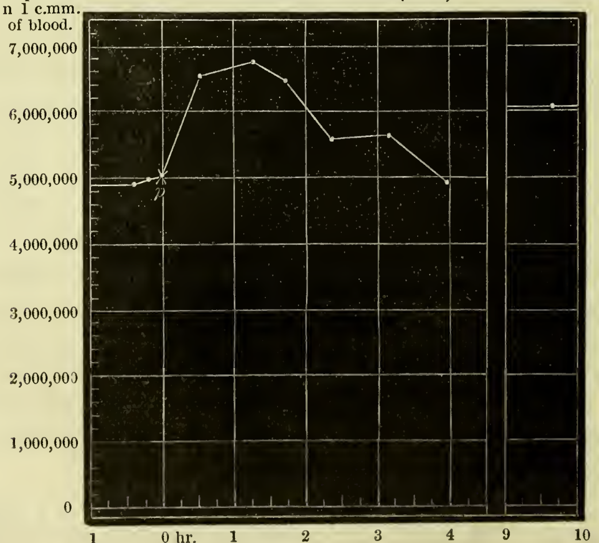
Gower's modification of Hayem's instrument was that used for measuring and diluting the blood and counting the corpuscles. Two separate enumerations of the corpuscles were always made, and in the first two experiments one of these enumerations was made by Dr. Logan, who kindly assisted me, and the other by myself. Ten of the microscopic square areas were always included in each counting.

Experiment LIV.—J. W., male, æt. 33. Partook of a light meal of bread and milk at 11 A.M. At 3.5 P.M. was placed in bed, and at

3.25 P.M. a drop of blood was withdrawn in the usual manner from the thenar eminence of the right hand. Care was taken that the skin of the hand was perfectly clean at the point punctured and free from moisture. If the blood did not come freely, it was never pressed out, as by pressure the interstitial fluid of the tissues was apt to be mixed with the blood; and if without pressure not more than a single drop oozed out it was rejected, and another and deeper puncture made; for, again, was there a chance of its contamination with the tissue-fluid from its slowly appearing. At 3.38 P.M. a second enumeration of the blood-corpuscles was made for the purpose of controlling the first, and two minutes afterwards a purgative dose of sulphate of soda in a concentrated form was administered. The blood was examined several times afterwards. All the corpuscles, both red and white, were counted, and the numbers obtained throughout the experiment were as follows:—

3.25 P.M.—4,850,000 corpuscles in each c.mm. of blood.
3.38 P.M.—5,020,000 " " "
3.40 P.M.—Administered 21·3 grammes ($\frac{3}{4}$ oz.) of sulphate of soda dissolved in 85 c.c. (3 oz.) of water, or about a 20 per cent. solution.
4.15 P.M.—6,540,000 corpuscles in each c.mm. of blood.
4.55 P.M.—6,790,000 " " "
5.20 P.M.—6,610,000 " " "
6 P.M.—5,710,000 " " "
6.45 P.M.—5,740,000 " " "
7.40 P.M.—4,930,000 " " "
7.45 P.M.—Dinner.
1 A.M.—6,020,000 " " "

EXPERIMENT LIV. (Man).



Showing the effect of the administration of a 20 per cent. solution of sulphate of soda on the concentration of the blood.

The first evacuation of his bowels occurred at 6 A.M. on the following morning, and three hours afterwards there was a second fluid dejection.

These numbers show that very shortly after the administration of the salt the blood has become highly concentrated, the result without doubt of the rapid loss of fluid which it has suffered during the action of the salt in the alimentary canal. The degree of concentration is remarkable, and reveals to what extent the quantity of the liquid constituents of the blood may be reduced without being manifested by any corresponding outwardly visible symptoms. If the enumerations were made correctly, and every care was taken to ensure that they were, and if the numbers of the corpuscles truly represent to what extent the blood has been deprived of its fluid, it can be readily calculated that the total quantity of the blood had become reduced at 4.55 P.M. from 1 to 0·73; and supposing the man weighed 140 lbs., and that 10 lbs., or the $\frac{1}{14}$th part of this weight, were blood, then 2·7 lbs. of fluid must have passed into the alimentary canal.

But what is almost as remarkable is the rapidity with which the blood has returned to its normal state of dilution. This it accomplishes within four hours after the administration of the salt, and without any fluid having been taken in the interval. We cannot believe that the fluid at first poured out by the blood into the alimentary canal was afterwards absorbed, else how did purgation occur next morning. The dilution of the blood is only to be explained by the concentrated blood abstracting water from the tissues, in virtue both of its concentration and of its endosmotic power having become increased by the presence of the absorbed sulphate of soda.

Another noteworthy point is the concentration of the blood an hour after midnight. This secondary concentration of the blood I have observed in all my experiments, and I believe it exists during the greater part of the day following the administration of the salt, and long after the salt has ceased to excite alimentary secretion, and is doubtless to be attributed to the diuresis created by the absorbed salt in the process of its elimination by the kidneys. The diuretic effect ought certainly to begin so soon as absorption of the salt occurs, that is, almost

immediately after administration; but it is probable that the absorption of the salt proceeds slowly, and its full diuretic action is not observable until after some time. Moreover, after the drain upon the blood by the salt within the intestines has has been arrested, the tissue-fluids will for a while be able to balance the diuresis; but, when the tissues begin to yield their fluid more slowly from their comparative exhaustion, the diuresis, proceeding with the same rapidity as previously, will lead to a concentration of the blood. The quantity of urine evacuated before and after purgation supports this view.

Day before the experiment, . . .	1596 c.c.
Day of the experiment, ...	1316 „
First day after the experiment, . . .	2240 „
Second day after the experiment, . .	1120 „

The next experiment was made a few days afterwards on the same individual. On this occasion a dilute solution of the same quantity of the salt was administered.

Experiment LV.—The blood was taken from the thenar eminence of the right hand as in the previous experiment. At 11 A.M. he was supplied with a light diet of bread and milk, and at 3.20 P.M. he was placed in bed and the experiment commenced. The following is the record of the various enumerations of the blood corpuscles before and after the administration of the purge.

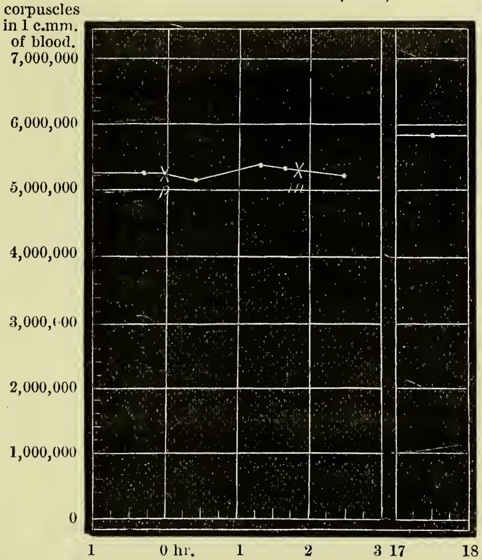
3.40 P.M.—5,250,000 corpuscles in each c.mm. of blood.
3.55 P.M.—Administered 21·3 grammes ($\frac{3}{4}$ oz.) of sulphate of soda dissolved in 227 c.c. (8 oz.) of water, followed immediately by other 227 c.c. (8 oz.) of water, altogether about a 5 per cent. solution.
4.20 P.M.—5,140,000 corpuscles in each c.mm. of blood.
5.10 P.M.—5,310,000 „ „ „
5.32 P.M.—5,300,000 „ „ „
5.40 P.M.—Free watery purgation.
6.22 P.M.—5,235,000 corpuscles in each c.mm. of blood.

Next morning and before breakfast:—
9.30 A.M.—5,830,000 corpuscles in each c.mm. of blood.

The dilute solution of the sulphate of soda, unlike the concentrated solution, caused no immediate concentration of the blood; but here, also, as with the other, there followed a remote hæmatic concentration, which was naturally to be expected if the explanation I have already given of this concentration be correct, an

explanation supported once more by the quantity of urine excreted.

Experiment LV. (Man).



Showing the effect of the administration of a 5 per cent. solution of sulphate of soda on the concentration of the blood. Purgative administered at *p*; purgation occurred at *m*.

Day before the experiment, . . .	1092 c.c.
Day of the experiment, ...	528 „
(The urine evacuated at 5.40 P.M., when purgation occurred, is not included.)	
Day after the experiment, ...	1736 „

A dilute solution of the salt passes, therefore, through the canal without, in so far as its purgative effect is concerned, producing any change in the volume of the blood. The remote concentration of the blood, due, as I believe, to diuresis, is, however, almost as evident as in the previous experiment.

We are warranted in concluding from these two experiments, contrary to the view expressed in the first series of experiments, that, at any rate, a concentrated solution of a saline purgative excites secretion within the alimentary canal sufficient to produce a marked diminution of the volume of the blood. Thus, by a method less open to objection than that employed in the

preceding series of experiment, we have arrived for the concentrated salt at the same result.

The two succeeding experiments are merely a repetition on the dog of those I had made on man, as I deemed it desirable to have confirmation of the interesting results obtained.

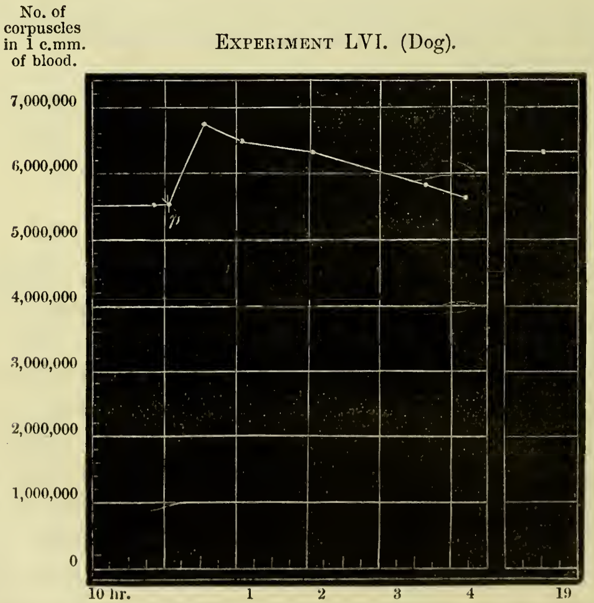
Experiment LVI.—Terrier bitch, weighing 6·12 kilogrms. No food on day of experiment. The outer surface of the calf of the right fore-leg was cleanly shaved, and from this, by puncturing with a sharp needle, sufficient blood was obtained for examination.

3.20 P.M.—5,530,000 corpuscles in each c.mm. of blood.
3.45 P.M.—Administered 12 grammes of sulphate of soda made into large pills with bread and a few drops of mucilage. This quantity dissolved in water had been found sufficient a week previously to purge the animal.
4.15 P.M.—6,730,000 corpusles in each c.mm. of blood.
4.45 P.M.—6,500,000 " " "
5.45 P.M.—6,380,000 " " "
7.20 P.M.—5,860,000 " " "
8 P.M.—5,680,000 " " "
8.10 P.M.—Fed as usual.

Next day, and before receiving food:—

10.45 A.M.—6,320,000 corpuscles in each c.mm. of blood.
5 P.M.—Fluid evacuation of the bowels.

EXPERIMENT LVI. (Dog).



Showing the effect of the administration of a 20 per cent. solution of sulphate of soda on the concentration of the blood. Purgative administered at *p*.

The result of this experiment is practically the same as that of Experiment LIV., except that the concentration of the blood is not quite so excessive.

Experiment LVII. —Same dog as in preceding experiment, but several days afterwards. No food on day of experiment. Blood taken from the same part of the body as before.

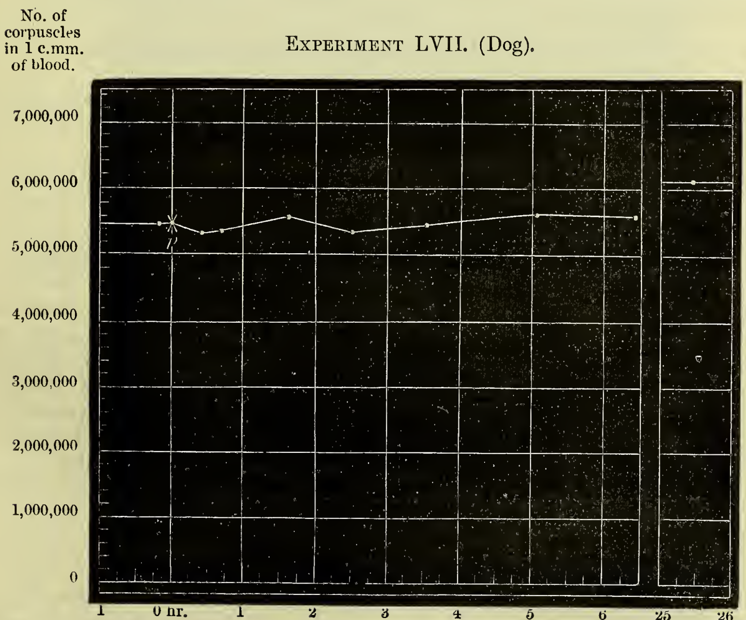
11.30 A.M.—5,490,000 corpuscles in each c.mm. of blood.
11.35 A.M.—Administered 12 grammes of sulphate of soda dissolved in water so as to form a 5 per cent. solution.
12 noon.—5,300,000 corpuscles in each c.mm. of blood.
12.23 P.M.—5,310,000 " " "
1.10 P.M —5,650,000 " " "
2 P.M.—5,350,000 " " "
3 P.M.—5,430,000 " " "
4,30 P.M.—5,720,000 " " "
6 P.M.—5,690,000 " " "
6.20 P.M.—Fed as usual.

Next morning, and before feeding :—

10.15 A.M.—6,110,000 corpuscles in each c.mm. of blood.

Purgation took place during the night.

EXPERIMENT LVII. (Dog).



Showing the effect of the administration of a 5 per cent. solution of sulphate of soda on the concentration of the blood. Purgative administered at *p.*

Here, again, as in the corresponding experiment on man, a

dilute solution of the purgative does not produce an immediate concentration of the blood, but does so after many hours.

From the next experiment, which concludes the present series, we learn that, if a dog be allowed no water for two days, the blood will become concentrated; and if, in this condition, a concentrated solution of a purgative salt be administered, little or no further concentration of the blood will occur, showing that in such a condition the blood is no longer capable of parting with its water to the secretion excited by the salt, or parts with it in a quantity insufficient to produce purgation. An explanation is thus offered of the results obtained from my first series of experiments.

Experiment LVIII.—Same dog as in the two preceding experiments. Fed for two days on stale wheaten bread; no water. No food on day of experiment. Blood taken from the same part of the body as previously.

Before the commencement of the water-restricted diet, the corpuscles in one c.mm. of blood numbered 5,510,000. On the third day of the special diet, they were as follows:—

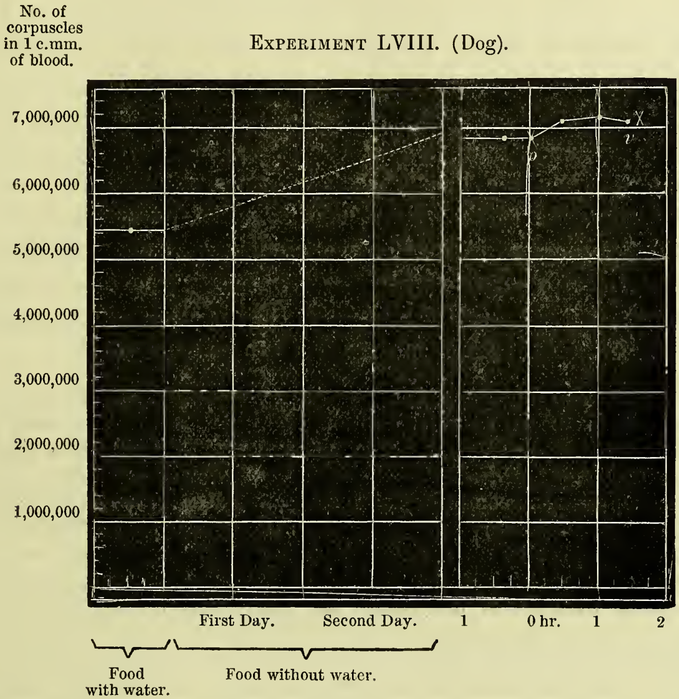
5.10 P.M.—6,910,000 corpuscles in each c.mm. of blood.
5.20 P.M.—6,800,000 ,, ,, ,,
5.35 P.M.—Administered 12 grammes of sulphate of soda made into pills with bread and a drop or two of syrup.
6.10 P.M.—7,130,000 corpuscles in each c.mm. of blood.
6.30 P.M.—7,210,000 ,, ,, ,,
6.55 P.M.—7,120,000 ,, ,, ,,
7.3 P.M.—Vomited between 20 and 30 c.c. of excessively tough, glairy, colourless fluid, a small portion being slightly tinged with blood. It was so viscid that, after standing for half an hour, it could hardly be poured out of the vessel in which it had been collected. It was mixed with a large quantity of undissolved crystals of the sulphate. The reaction was acid, but not so strongly acid as the gastric juice usually is.

Purgation never occurred, although water was given to the dog immediately after it vomited.

The blood, notwithstanding its previous concentration from a restricted water-supply, loses a small portion of its fluids, probably as much as the salt has required for its solution and absorption. The pill form in which the salt was given did not, I think, delay its action, as the pills were made only a few

minutes before administration, and were very friable, breaking down with the gentlest pressure.

EXPERIMENT LVIII. (Dog).



Showing the effect on the concentration of the blood,—of (1) abstinence from water, and (2) the administration during this condition of a purgative dose of sulphate of soda in a concentrated form. Purgative administered at *p*; vomiting occurred at *v*.

The result of this experiment explains how, in the first series of experiments, purgation failed to be produced by the administration of a concentrated solution of a saline purgative to an animal which had received no water for two days previously. By the restriction of water in the diet, not only was the alimentary canal emptied of its fluids, but the blood was also greatly concentrated. And, notwithstanding Experiment XXIX., where, indeed, a little purgation did occur, I am strongly inclined to think that the concentration of the blood was a much more powerful factor in the prevention of purgation than the absence of fluid in the alimentary canal. A single night's fasting is sufficient to deprive the canal of fluid, as I have ascertained whilst making the experiments of the succeeding series; and

after so short an abstention from water, I have never found that cats were to any extent less powerfully purged by a concentrated solution of the salt than by a dilute solution, although it has been proved in Series A. that the former failed to act when water was withheld from the animal for two days or more. This implies, indeed, that the method employed in Series A is not satisfactory, but it still leaves us the very interesting fact, that when the blood becomes concentrated it no longer yields secretion to the stimulus of a saline purgative applied to the mucous membrane of the alimentary canal. It would appear to be otherwise when the secretion is the result of inflammatory irritation, if the result of the experiment with croton oil (Experiment XXX.) can be proved to be constant.

In justice to M. Brouardel, I ought to mention that he has preceded me in the study of the action of cathartics on the concentration of the blood, although I was not aware of the existence of his paper (*L'Union Médicale,* No. 110, t. xxii.) when I made the above experiments. The conditions of his experiments are, however, so lax, that the absence of any account of them in physiological and pharmacological text-books is readily understood. His investigation was conducted on patients in the hospital of St. Antoine. The purgatives employed were castor oil, croton oil, jalap, and in one instance a saline solution (Eau de Sedlitz), and the degree of concentration of the purgative was not attended to. The blood was examined some time in the afternoon, and apparently without regard to the effect of ordinary meals on its concentration. The purgative was shortly afterwards administered, and the blood was not again examined until some time on the following day, so that the concentration he observed was that which I have pointed out as secondary and not immediately dependent on the cathartic action of the salt. Moreover, in nearly every case, eight altogether, his patients were suffering from diseases which might of themselves have seriously affected the condition of the blood when under the influence of purgatives—heart disease and anasarca in two cases, prolonged constipation (eight days, &c.), in four others. He adds, in opposition to Ch. Robin,[1] that purgatives diminish instead of notably augmenting the number of the white corpuscles in the blood.

[1] Ch. Robin, *Leçons sur les humeurs normales et morbides*, Paris, 1867, p. 52.

Series of Experiments, D.

The effect of the salt on the alimentary canal, and the absorption of the salt from the canal, as ascertained by killing the animals at stated intervals after its administration by the mouth, and measuring the fluid in the canal, and estimating the quantity of salt present.

The methods by which I have arrived at the conclusion that a purgative salt excites secretion within the alimentary canal are those of the two preceding series of experiments. The former of these methods is not without objection, as I have more than once admitted, although I have attempted at some length to define in how far the conditions of the method modify the action of the salt. And it may be urged against the latter method that the relative increase of the blood-corpuscles is no direct or positive proof of the serum being diminished; we merely infer that there is diminution of the latter, because we do not believe it possible that the total number of the corpuscles in the blood can be as suddenly increased as the results of the B. Series of Experiments would otherwise imply.

I have now to describe a method, which, from its extreme simplicity and the absolute normality of its conditions, is free from every objection. It suggested itself to me in the course of my experiments on the exposed intestines of the cat. In these it will be remembered that the animal received no food of any kind on the day of the experiment, nor for more than twenty hours previous to the operation, and that the diet was uniform in kind and quantity for at least a week previously; care also was taken to observe that the fæces had been for some days of their natural firm consistence. Under these conditions I had frequent opportunity of observing the state of the alimentary canal of the various cats operated upon. And I always found that on opening the abdomen the small intestine in its whole length was completely collapsed and appeared perfectly empty; and, if I attempted to press out the contents of the intestine through the incisions made for washing it, never more than one or two drops of mucus escaped, mixed now and then with a small quantity of brownish shreds of undigested food, and fre-

quently with fragments of tape-worms. Or, if I laid open the whole length of the alimentary canal, as I did on more than one occasion when the animal was killed intentionally or accidentally by an overdose of chloroform, the canal was practically empty excepting the large intestine, which always contained more or less of brown firm fæces. The total quantity of mucous fluid found in the stomach and small intestine never exceeded 5 c.c., and was in most cases practically *nil*. The contents of the colon were always firm, and quite as hard as evacuated fæces. In all my experiments, where the intestine was ligatured and injected, and the animal killed after a certain number of hours, the condition of the remainder of the canal was always carefully observed and noted after death. In looking over these protocols I found that the stomach usually contained from 1 to 2 c.c. of yellowish fluid of an alkaline reaction, or very rarely acid. Only in one instance did the quantity of the fluid attain 5 c.c. From the whole length of the small intestine, excluding of course the part operated on, one or two drops of mucus were generally obtained, and on no occasion more than half a cubic centimetre. The contents of the colon were as described. I therefore felt perfectly warranted in concluding that the alimentary canal of a healthy cat contains virtually no fluid twenty to twenty-four hours after a meal. Now, if a saline purgative be administered to a cat in this condition, it is evident that by killing the animal at stated intervals afterwards and ascertaining the amount of fluid in the canal, it will be possible to obtain a fairly accurate estimate of the quantity of secretion excited by the salt, if secretion does actually take place. There is no disturbing element in the form of any vivisective operation. This method further promised, by the opportunity it gave me of analysing the quantity of the salt recoverable from the alimentary canal, the means of ascertaining with what rapidity the salt was absorbed, and whether or not it underwent the remarkable variations in quantity—first being absorbed and afterwards excreted—which Headland mentions, and to which I have fully alluded.[1]

The details of the method employed in each of my experi-

[1] P. 4.

ments hardly require description after what I have just said. The cat, for cats were always used, was fed regularly on a stated quantity of boiled flesh for at least a week previously, the condition of the fæces being observed, and the animal rejected if the excrement was in the smallest degree more soft than normal. The last meal was given on the day preceding, and not later than twenty hours before, the experiment. During this interval water, as well as food, was withheld from the animal. The experiment began with the injection of the solution of the purgative salt into the stomach; and this was made through a vulcanised tube passed down the œsophagus, so that no part of the solution was lost. As the cat was extremely apt to vomit shortly afterwards, its attention had to be distracted for half an hour or longer by frequent stroking. Even in spite of this it often vomited, and delayed for a few days the experiment. At the expiry of the desired interval, if purging had not previously taken place, which was not unfrequently another source of delay, the cat was killed as in former experiments. As the fluid fæces were extremely apt to escape from the anus during the struggles which preceded death, special care had to be taken that none was lost. This was best effected by transfixing and ligaturing the anus immediately after stunning the cat. In some cases, where the amount of fluid in the various portions of the alimentary canal was to be ascertained unaffected by the changes produced by the convulsions of the whole muscular system which preceded death, the abdomen was at once opened after tying the anus and before the animal died, but whilst it was unconscious, and ligatures were placed round the canal at various points. The fluid present in the canal was measured along with what solids it might contain. These in the fluid from the small intestine were never more than fragments of tape-worms; in the large intestine, a quantity of solid fæces. The contents of the large intestine were evaporated to dryness over the water bath; and, by adding to the weight of the residue the proportion of water which the ordinary unevacuated fæces contained, I had the means of ascertaining with considerable exactness to what extent the quantity of the fluid had been increased by the normal contents of the colon. The percentage of water in the normal contents of the colon I

estimated in several other cats, and found it to be fairly constant. These estimations I now give:—

Total Weight of the Contents of the Colon.	Weight after drying at 100° C.	Percentage of Water.	Quantity of H_2SO_4 as $Na_2SO_4.10H_2O$.
grms.			grms.
4·34	1·516	65	0·016
4·34	1·448	67	...
10·27	3·321	68	...
3·72	1·338	64	...
3·91	1·408	64	...
9·541	3·564	66	0·063
12·804	3·100	76	0·101

The average percentage of water in these seven different quantities of unevacuated fæces is 67·1 per cent. As this proportion of water in normal fæces is not absolutely definite and invariable, and, as the average obtained may have been a little too high from the exceptionally large percentage in the last quantity of fæces, I have for convenience considered the usual percentage to be 66·6, which allows of the weight of the fæcal matter in the colon being obtained from the evaporated residue by simply multiplying the weight of the latter by three. Where the purgative salt is mixed with the fæces, its weight must, of course, be estimated and deducted from the total residue before trebling. The weight of the contents of the colon were thus ascertained, and, by subtracting it from the total quantity of fluids and solids in the alimentary canal, it was easy to gain a tolerably correct notion of the quantity of the secretion excited by the administered salt.

In order to estimate the quantity of the salt in the alimentary canal, the canal from the cardiac orifice of the stomach to the lower end of the rectum was removed from the abdomen, slit open in its whole length, and infused repeatedly—generally eight to ten times during three or four days—in distilled water. The various infusions were mixed and evaporated to dryness; and the residue, added to that previously obtained from the contents of the canal, was sprinkled, unless where the sodium was estimated when lime was used, with a small quantity of dried carbonate of soda, and burned. The ash was dissolved in

hydrochloric acid, and the sulphuric acid estimated by the usual method.

From a number of experiments given in an earlier part of this paper,[1] I concluded that 5 grammes of crystalline sulphate of soda was a dose sufficient to purge with certainty a cat of average weight. The cats selected were, as much as possible, of similar weight, full-grown, and well-conditioned.

The first three experiments were made principally with the intention of observing the effect of different degrees of concentration of the salt on the amount of the fluid within the canal.

Experiment LIX.—Cat, male, weighing 3·28 kilogrammes. Injected *per os* into the stomach 5 grammes of sulphate of soda dissolved in 100 c.c. of water, or a 5 per cent. solution. Killed exactly *one hour* afterwards.

Autopsy.—The stomach contained 1·5 c.c. of alkaline, transparent, colourless, frothy mucus. The small intestine, which was 141 cm long, contained 24 c.c. of a brownish fluid, mixed with fragments of several large tape-worms; reaction also alkaline. In the colon and rectum there were only 2 c.c. of a thin brown fluid. The remainder had escaped from the anus while the animal was dying, but was carefully collected by holding a porcelain basin beneath; for during my first experiments I had not employed the method of ligaturing the anus. The evacuated material consisted of a mixture of firm fæces with a large amount of watery liquid, and measured 87 c.c. The colon and rectum were 19 cm. in length. No part of the mucous membrane of the intestines exhibited any congestion which could be attributed to the action of the purgative: a few small reddish spots, but apparently of long standing, and probably caused by the tape-worms, were observable in the upper part of the small intestine; otherwise, the mucous membrane was perfectly pale throughout both stomach and intestines.

The residue obtained after evaporation of the fluid weighed 6·914 grammes, and the ash, less the carbonate of soda, 2·793 grammes. From this ash, which included that of the infusions, was recovered sulphuric acid equivalent to 2·488 grammes of $Na_2SO_4.10H_2O$, which corresponds to 1·097 grammes of the water-free salt. Deducting the latter weight from the ash, we obtain 1·696 grammes, or the amount of the ash of the contents of the canal apart from that added by the sulphate. If from 6·914 grammes, the weight of the evaporated residue, be taken 2·488 grammes, or the amount of the crystalline sulphate of soda recovered, there remain 4·426 grammes, or the real

[1] P. 19.

weight of the water-free solids of the fluid. This, multiplied by three, gives approximately the quantity of faecal matter in the colon previous to the administration of the purge, which quantity—reckoning each gramme as equivalent to a cubic centimetre—deducted from the total quantity of the contents found in the alimentary canal, leaves 101·22 c.c. as the amount of fluid due to the presence of the purgative salt. The specific gravity of the fæces, which was in several cases estimated, is so little above that of water, as to justify ignoring the difference in deducting the weight of the fæces from the bulk of the fluid.

This experiment brings out three, perhaps four, noteworthy points. The amount administered of the 5 per cent. solution of the salt has neither increased nor diminished during the hour it was in the alimentary canal. Yet half of the salt has disappeared, proving that absorption must have been active, but equalled by secretion. Further, the mucous membrane is uncongested, and the secretion is therefore not the result of inflammatory irritation. Lastly, deducting the weight of the water-free salt from that of the ash of the intestinal contents, we perceive that there is a remarkably large percentage of ash in the fæces and purgative secretion,—36 per cent. of the solids,—which corroborates the statement I previously made as the result of the first series of experiments, that the saline purgative, apart from its own presence, greatly increases the quantity of salts in the fæces.

Experiment LX.—Black cat, male, lean, weighing 2·33 kilogrammes. As the cat was smaller than the last, I administered a less dose. 40 c.c. of a 10 per cent. solution of sulphate of soda, or 4 grammes of the salt, were injected into the stomach. Killed *one hour* afterwards.

Autopsy.—On opening the abdomen immediately after death, there was no visible outward congestion of the intestines, and no excitement of peritalsis, more than is ordinarily observed after death. The stomach contained 1 c.c. of mucus, and the small intestine 11 c.c. of a brownish viscid fluid, consisting largely of tape-worms mixed with a few undigested shreds of food; and the large intestine contained, including what was evacuated during the death-struggles, 76 c.c. of a mixture of hard lumps of fæces with thin brown fluid of alkaline reaction. The mucous membrane of the duodenum, commencing at the pylorus and extending downwards for about 17 or 18 cm., was marked with a considerable number of little arborescent injections of minute blood-vessels. The small intestine was 116 cm. long, and the large intestine 18 cm.

The evaporated residue of the contents of the intestines, evacuated and unevacuated, weighed 6·157 grammes, and the quantity of sulphuric acid, recovered from this and the infusions of the canal, amounted to 2·454 grammes, calculated as $Na_2SO_4.10H_2O$. Deducting the solid contents of the colon, the 40 c.c. of injected salt solution had therefore increased to 76 c.c.

There is much stronger evidence in this than in the preceding experiment that the salt excites secretion. This is dependent on the greater concentration of the solution administered. The 10 per cent. solution has almost doubled itself within the space of an hour, while more than one-third of the salt has been absorbed. The reddish arborescent spots in the duodenum are not to be regarded as due to the action of the salt. They are either caused by the tape-worms present, or by a chronic duodenal congestion which is not uncommon in cats. For, in several animals killed without the previous administration of a saline purgative, or indeed any drug, I have often observed the same appearance, especially when tape-worms were present as they so constantly are. Had the congestion in the last experiment been produced by the salt, it would in all probability have been diffuse and not maculate and arborescent, and would have extended down the jejunum.

Experiment LXI.—Cat, male, weighing 2·95 kilogrammes. Administered 25 c.c. of a 20 per cent. solution of sulphate of soda, or 5 grammes of the salt. Killed at the end of *one hour.*

Autopsy.—The stomach contained 0·3 c.c. of colourless, viscid, frothy mucus, with an alkaline reaction. The small intestine contained 22 c.c. of a viscid fluid, well mixed with a large quantity of yellowish-white flocculi and fragments of tape-worms, and a few particles of brownish matter. The fluid, where free from flocculi, was transparent and colourless, and apparently contained no bile. The absence of bile was confirmed by the fluid exhibiting no play of colours with strong nitric acid. The reaction of the fluid was alkaline, and 10 c.c. of it required 0·125 c.c. of the pharmacopœial standard solution of oxalic acid for its neutralisation. The acid solution was diluted as explained in the second series of experiments.

The diastatic power of the fluid was ascertained. 2 c.c. of the transparent colourless portion of the fluid from the small intestine were mixed with a 2 per cent. solution of starch, and allowed to digest for forty-eight hours. Neither of the original fluids contained sugar. At the end of this time the mixture contained 0·265 gramme of maltose, as estimated by Pavy's modified Fehling. 5 c.c. of the intestinal fluid would, therefore, have produced 0·662 gramme of maltose.

5 c.c. of blood were drawn from the vena cava immediately after death, and were also mixed and digested with a 2 per cent. solution of starch. In forty-eight hours 0·411 gramme of maltose was formed. Before estimating the sugar, the albumen was removed by acidification, boiling, and filtration. The intestinal fluid was, therefore, hardly more active than blood in the digestion of starch, and could not have contained more than the merest trace of the pancreatic juice.

As a large discharge had taken place from the rectum immediately previous to death, the colon and rectum were found to be almost empty. Their contents, along with the evacuated fluid, measured 71 c.c., and consisted of the usual mixture of brown solids and fluids; the reaction was neutral. The residue obtained by evaporation weighed 5·767 grammes. The quantity of sulphuric acid, reckoned as $Na_2SO_4.10H_2O$, recovered from the whole contents of the alimentary canal and from the infusions, accurately allowing for what was used for digestive purposes, amounted to 2·766 grammes. The 25 c.c. of salt solution injected had increased to 84 c.c.

The mucous membrane of the stomach was very slightly congested, but that of the intestines was perfectly pale in its whole extent.

In this experiment the 20 per cent. solution administered has much more than trebled itself. And there cannot now be the shadow of a doubt, when we consider the results of these three experiments, that a solution of sulphate of soda stronger than 5 per cent. excites secretion within the alimentary canal. There is also every reason to assume, from the nearly equal absorption of the salt in all of the experiments, that even a 5 per cent. solution excites secretion almost as copiously as a 20 per cent. solution, although in the former case, on account of the greater dilution of the salt, absorption from the canal is less hindered, and consequently the bulk of the saline solution is not increased as in the latter case. Thus, by the most unobjectionable of methods, I venture to think I have indisputably established that a saline purgative stimulates secretion within the alimentary canal; and it would appear from the last experiment that the secretion is derived from the canal itself and not from the pancreas or bile. The rapidity of the purgative action and of the absorption of the salt is also remarkable.

The next experiments were mainly intended to elicit the course of action of the salt, the cats being killed at various periods after the administration of the salt.

Experiment LXII.—Cat, female, weighing 2·60 kilogrammes. Administered 25 c.c. of a 20 per cent. solution of sulphate of soda, or 5 grammes of the salt. Killed *fifteen minutes* afterwards.

Autopsy.—The abdomen was opened, and ligatures placed round the pylorus, jejunum, and cœcum immediately after the animal was stunned, and before any convulsive spasms had occurred. The stomach contained 29 c.c. of a colourless, slightly opalescent, limpid fluid, *alkaline* in reaction. Its opalescence increased on heating, and the application of other proteid reactions proved the presence of a distinct trace of albumen. The duodenum contained 1 c.c. of a viscid yellowish fluid, and the jejunum 7 c.c. of a colourless, almost transparent liquid. In the ileum were 2 c.c. of a viscid, colourless fluid. The colon contained no fluid, only the usual firm fæcal matter. The mucous membrane of the stomach was slightly congested; that of the duodenum and of the upper part of the jejunum, extending for about 42 cm. from the pylorus, was diffusely and markedly congested. Out of many experiments, this is the only occasion on which I observed a diffuse and acute congestion of the intestinal mucous membrane after the action of the salt, even when an equally strong solution was administered, and the animal killed within an equally short period.

The gastric fluid, including an infusion of the stomach-wall, yielded 3·546 grammes of $Na_2SO_4.10H_2O$, as calculated from the sulphuric acid recovered. As from other experiments, which will be afterwards given, I learned that the sulphate is absorbed with extreme slowness by the stomach, I concluded that a part of the salt solution had passed into the intestine, even were the presence of fluid there no indication of an escape from the stomach. And it is probable that this escape had taken place immediately before the animal was killed. For, assuming on good grounds that the stomach had not absorbed more than a quarter of a gramme of the salt, and that the remainder of the salt was distributed over 39 c.c. of fluid, or the total quantity found in the stomach and intestines, we would expect to find in 29 c.c. of the fluid, or the quantity in the stomach, 3·54 grammes of the salt, or exactly the amount recovered. And, as from this calculation the intestinal fluid must have contained the same proportion of salt, the salt solution could not have been more than a very few minutes within the intestine, or it would have lost much of its salt by absorption and increased rapidly in bulk, as I have ascertained from previous experiments.

The important conclusion from this experiment is that the salt, when administered in the form of a 20 per cent. solution, is capable of withdrawing from the stomach a tolerably large amount of secretion. The increase to 39 c.c. of the 25 c.c. administered must be mainly attributed to the secretion supplied by the stomach. It is otherwise when the salt solution is not stronger than 10 per cent., as a future experiment will prove.

Experiment LXIII.—Cat, male, weighing 4·30 kilogrammes. Injected into the stomach *per os* 25 c.c. of a 20 per cent. solution of

sulphate of soda. Killed *twenty minutes* afterwards. As in the preceding experiment, the abdomen was opened and the canal ligatured at various points immediately after stunning the animal.

Autopsy.—The stomach contained 1 c.c. of a colourless, transparent, slightly acid fluid, and the small intestine, 9·5 c.c. of a colourless, or faintly yellowish, opaque fluid, with an alkaline reaction. In the large intestine were 79 c.c. of a brownish watery fluid, mixed with hard fæcal lumps. The mucous membrane of the stomach was slightly congested, at least was of a dusky hue, towards the pylorus. In the upper part of the small intestine was a number of irregular congested spots or patches, which were evidently chronic in nature. Nearly a dozen of tape-worms were removed from the intestine. The rest of the mucous membrane of the intestines was perfectly pale. The small intestine was 162 cm. long.

The contents of the colon, after evaporation, weighed 6·661 grammes, and, along with the other fluids and with the infusions, yielded 4·526 grammes of $Na_2SO_4.10H_2O$, reckoned from the sulphuric acid recovered. The amount of fluid due to the presence of the salt was 74·4 c.c.

The great rapidity with which the salt solution has increased from 25 c.c. to 74 c.c. is very remarkable, this having been accomplished within twenty minutes. On the other hand, comparatively little of the salt has been absorbed. Half a gramme of salt absorbed, and 50 c.c. of fluid secreted, show such a proportion of salt to secretion which quite precludes the supposition of many investigators[1] that the secretion is due to the osmotic power of the salt. The endosmotic equivalent[2] of crystalline sulphate of soda is 11, and half a gramme of the salt should have caused a secretion of only 5 or 6 c.c. The same form of argument against the salt acting osmotically applies with hardly less cogency to Experiment LXII. and even to Experiment LXI.

Experiment LXIV.—Cat, female, weighing 2·55 kilogrammes. Administered 25 c.c. of a 20 per cent. solution of sulphate of soda, equivalent to 5 grammes of the salt. Killed *half an hour* afterwards, and the alimentary canal ligatured at pylorus, middle of jejunum, and cœcum, immediately after stunning.

Autopsy.—The stomach contained 17 c.c. of a clear acid fluid, along with a piece of well-nigh completely digested meat,[3] about twice or

[1] P. 2. [2] Aubert, *op. cit.*

[3] As I afterwards ascertained, the cat had obtained this by accident early in the morning.

three times the size of a filbert. The duodenum and upper half of the jejunum contained 8 c.c. of a colourless (untinged by bile), opalescent, limpid fluid, of a slightly acid reaction. In the lower part of the jejunum and in the ileum were 14 c.c. of a colourless fluid, mixed with a few brownish particles of ingesta; alkaline in reaction. In the colon and rectum, exclusive of solid fæces, there were 10 c.c. of fluid.

All the fluids, mixed with the infusions of the canal and of the food in the stomach, yielded 3·412 grammes of $Na_2SO_4.10H_2O$, estimated from the sulphuric acid present. The 25 c.c. injected had, therefore, increased to 49 c.c.

The mucous membrane was everywhere pale, excepting one or two irregularly disposed and slightly congested spots in the duodenum close by the pylorus.

The increase of the salt solution is not so great as in previous experiments, and has doubtless been modified by the presence of a small quantity of food in the stomach. It is worthy of remark that, while the fluid in the stomach and upper half of the intestine is still acid, it has become alkaline in the lower half. The acidity of the latter has been neutralised by the alkaline intestinal secretion, and not by the bile or pancreatic juice. For if it had been effected by the latter, the change in reaction would have been observable so soon as the fluid had passed beyond the point of entrance of these secretions in the duodenum; and, therefore, the fluid in the upper half of the intestine ought also to have been alkaline. This is another proof of the opinion already advanced, that the bile and pancreatic juice contribute practically nothing to the secretion excited by the salt.

Experiment LXV.—Cat, male, weighing 2·95 kilogrammes. Injected into the stomach *per os* 50 c.c. of a 10 per cent. solution of sulphate of soda, or 5 grammes of the salt. Killed *two hours, ten minutes* afterwards.

Autopsy.—The stomach contained 2 c.c. of a frothy yellowish fluid, alkaline in reaction. In the small intestine were 20 c.c. of thick mucus, largely mixed with tape-worms, and also of a yellowish colour. The contents of the colon, which was fully distended, measured 83 c.c., and consisted in part of hard fæcal masses; reaction neutral. Evaporated to dryness, the residue weighed 8·942 grammes, and, with the residues of the other fluids and of the infusions, yielded sulphuric acid equivalent to 3·724 grammes of $Na_2SO_4.10H_2O$. The 50 c.c. originally injected had, therefore, after deducting fæces, increased to 89 c.c.

The mucous membrane of the stomach was covered with viscid yellow mucus, but was quite free from congestion. The small and

large intestines showed also no trace of congestion unless in the upmost 20 cm., where a slight degree of chronic congestion was visible.

Comparing this experiment with Experiment LX., and allowing for the difference in the dose of the salt, we observe that the salt solution has undergone no material change in bulk since the end of one hour, and, it may be, even a much shorter period, after its administration. The maximum of the bulk of the saline fluid within the canal is, therefore, early attained.

The quantity of the salt recovered in this experiment calls much more for our attention. We have formerly seen that the amount of the salt within the canal gradually decreases from the time of its administration until one hour afterwards. In this experiment we find it at the end of two hours on the increase. Instead of the $2\frac{1}{2}$ grammes, recovered in the three experiments, where the animal was killed at the end of one hour, we have roughly $3\frac{3}{4}$ grammes. Such a curious and important phenomenon required confirmation, and accordingly the next experiment is simply a repetition of the last.

Experiment LXVI.—Cat, male, weighing 3·05 kilogrammes. Administered 50 c.c. of a 10 per cent. solution of sulphate of soda, equivalent to 5 grammes of the salt. Killed after *two hours.*

Autopsy.—The intestines, exposed immediately after death, were pale, and exhibited extremely little movement. The stomach contained a drop of yellowish, alkaline mucus; the small intestine 32 c.c., chiefly in the ileum, of a perfectly colourless, limpid, alkaline fluid, with a small deposit of mucus. The colon was distended with 70 c.c. of a brown-coloured mixture of fluid and of solid fæces, also alkaline in reaction. The mucous membrane of every part of the canal was uncongested, unless in the duodenum, 20 cm. of which were marked with a few irregularly disposed patches of chronic congestion. There was a moderate number of tape-worms in the small intestine. The gall-bladder was well distended with bile.

The contents of the intestines yielded, after evaporation to dryness, a residue weighing 10·173 grammes, which, with the infusions, was found to contain 4·078 grammes of $Na_2SO_4.10H_2O$, calculated from the sulphuric acid recovered. The fluid originally administered had increased to 83·71 c.c. As the ash of the residue, deducting the sulphates, weighed 1·982 grammes, there must have been a large proportion of salts in the secretion excited by the purgative. The small intestine was 170 cm. in length.

This experiment fully attests the remarkable result of the

previous experiment, exhibiting even a larger amount of salt within the canal after the lapse of two hours.

In order to ascertain, at still later periods, what variations in quantity the salt suffered, was the object of the succeeding experiments.

Experiment LXVII.—Cat, male, weighing 2·72 kilogrammes. Administered 50 c.c. of a 10 per cent. solution of sulphate of soda, or 5 grammes of the salt. Killed after *three hours.*

Autopsy.—On exposing the intestines immediately after death, they appeared abnormally pale. After a few minutes' exposure, however, the blood-vessels ramifying on the peritoneal surface of the gut dilated, and imparted quite a congested aspect to the intestines. I mention this, as it was observed in almost every experiment; and it might lead some other investigator, who neglected to perceive the early uncongested stage, to the belief that the after redness was due to the action of the salt. Vulpian,[1] without doubt, failed to allow for this error in his experiments.

The stomach was practically empty, containing barely a drop of mucus. The contents of the colon and the lower part of the ileum measured 86 c.c. The upper part of the intestine was empty. The mucous membrane of the upper third of the small intestine was slightly congested, especially towards the pylorus, and in appearance and situation the congestion corresponded exactly to what I have so often seen in cats where no salt had been administered.

The fluids and infusions of the whole alimentary canal yielded 2·984 grammes of $Na_2SO_4.10H_2O$, reckoned from the sulphuric acid recovered.

From the second to the third hour after its administration the salt apparently begins once more to decrease in amount.

Experiment LXVIII.—Cat, male, weighing 2·72 kilogrammes. Administered 50 c.c. of a 10 per cent. solution of sodic sulphate, or 5 grammes of the salt. Killed *four hours* afterwards. Ligatures were placed round the alimentary canal at various points immediately after the animal had been stunned.

Autopsy.—The stomach contained 4 drops of bilious fluid; the small intestine, 3 c.c. of a yellowish-brown fluid, with an alkaline reaction. In the large intestine were 71 c.c. of a thin, brownish, gruel-like fluid, with the fæcal lumps much more disintegrated than in the previous experiments; reaction, neutral or faintly alkaline. The mucous membrane of the small intestine was very slightly and irregularly congested in its upper third. In the rest of its extent both in small and large intestines, it was perfectly pale.

The contents of the intestines, evaporated to dryness, weighed

[1] Vulpian, *op. cit.*

5·242 grammes, and, along with the infusions, yielded 3·072 grammes of $Na_2SO_4.10H_2O$, as estimated from the sulphuric acid present. The 50 c.c. of salt solution administered had, therefore, increased to 70 c.c.

This concludes the first portion of the experiments made by this simple method. They were performed with the greatest care, and every precaution was taken to ensure that, in the amount of the recovered sulphate given, all of it that could be procured from the alimentary canal and its contents was represented. They and the remaining experiments of the series were, although they may hardly seem so, the most tedious of all the experiments of this investigation, mainly owing to the time required for the extraction of the salt from the alimentary canal by repeated infusion, and for the perfect drying of the intestinal contents; and, as previously mentioned, the vomiting of the administered salt by the cat, or its being purged before the requisite time had expired, was a frequent source of delay. The results of the experiments are, however, of great interest. The indubitable proof they offer of the salt withdrawing fluid from the blood through exciting secretion in the alimentary canal I have already referred to. And we may hold it as settled that every solution of sulphate of soda stronger than 5 per cent., administered to a cat which has fasted for twenty hours, increases in quantity until its bulk roughly corresponds to the amount of fluid necessary to form a 5 per cent. solution of the dose of the salt originally administered. This maximum is rapidly reached, generally within less than an hour, and begins afterwards to gradually sink, from absorption being more active than secretion.

The secreted fluid was on almost every occasion examined for albumen, and never more than a mere trace could be detected. This is strongly opposed to the secretion being of the nature of an exudation or a transudation. The opposition is strengthened by the uncongested condition of the mucous membrane. The small patchy congestion of the duodenum frequently described is no proof, as I have already discussed, of the irritative action of the salt, as it is often met with in cats to which nothing has been administered, and is evidently either caused by tape-worms, or by repeated physiological arterial engorgements of this part of the canal, or even by a chronic

catarrhal condition. It is obviously chronic. When the congestion was acute and diffuse, as in one experiment (LXII.), I admit the salt may have produced it, but only when in the form of a concentrated solution, as it was in that experiment. And this effect is even exceptional after the application of a 20 per cent. solution, and I have never once observed it after a 10 per cent. solution. The secretion, therefore, cannot be regarded as an inflammatory exudation, as Vulpian has asserted.

The rapid passage of the saline fluid through the alimentary canal is also worthy of observation. Where the animal is fasting, almost the whole fluid reaches the colon within an hour, and at no period is much of it met with in the small intestine. The bulk of it is either in the stomach or the colon. If it has left the former, it passes without much delay through the small intestine to the latter. And if purgation does not at once occur, it is either owing to the inhibitory power exercised by the animal, or to the hardened fæces blocking the rectum and requiring disintegration. The passage of the salt will, doubtless, be much hindered when it is administered with food. The rapid action of a saline purgative, when taken in the early morning before breakfast, is easily understood from these experiments.

Much the most interesting result, however, is the remarkable variations in the quantity of the salt in its passage through the alimentary canal—the rapid absorption of nearly half the salt during the first hour after its administration, and the excretion of a considerable portion of the absorbed salt during the next hour, followed by a steady slow absorption of the salt until defæcation occurs. The annexed table brings this clearly out. In these changes we appear to have confirmation of Headland's statement,[1] now almost forgotten, and perhaps never credited, that the salt is absorbed by the stomach and the upper part of the intestine, and having reached the blood is carried by the circulation through the vessels of the glands of the lower part of the small intestine and colon, and in the act of being excreted by the glands excites them to increased secretion. If Headland's view be correct, we would expect the salt to purge equally, if not more powerfully, when injected directly into the

[1] *Supra*, p. 4.

SHOWING QUANTITY OF SALT AND FLUID WITHIN ALIMENTARY CANAL AFTER ADMINISTRATION OF SULPHATE OF SODA.

No. of Exper.	Weight of Cat.	Dose of Sodic Sulphate.	Strength of Solution of Salt.	Time after Administration.	Quantity of Contents (including Solids) of				Weight of Evaporated Residue.	Weight of Sod. Sulph. ($Na_2SO_4.10H_2O$) recovered.[1]	Weight of Residue, less Sod. Sulph.	Weight of Fæcal Matter.	Fluids, less Fæcal Matter.	Increase over Fluid administered.
					Stomach.	Small Intestine.	Colon.	Total.						
	kilogrs.	grms.	p. c.		c.c.	c.c.	c.c.	c.c.	grms.	grms.	grms.	grms.	c.c.	c.c.
LXII.	2·60	5	20	¼ hr.	29	10	...	39	...	3·546 [2]	...	...	39	14
LXIII.	4·30	5	20	20 m.	1	9·5	70	80·5	6·661	4·526	2·035	6·105	74	49
LXIV.	2·55	5	20	½ hr.	17	22	10 [3]	49	...	3·412	...	...	49	24
LIX.	3·28	5	5	1 hr.	1·5	24	89	114·5	6·914	2·488	4·426	13·278	101	1
LX.	2·33	4	10	1 hr.	1	11	76	88	6·157	2·454	3·703	11·109	77	37
LXI.	2·95	5	20	1 hr.	0·3	22	71	93·3	5·767	2·766	3·001	9·003	84	59
LXV.	2·95	5	10	2 hrs.	2	20	83	105	8·942	3·724	5·118	15·354	90	40
LXVI.	3·05	5	10	2 hrs.	0·1	32	70	102	10·173	4·078	6·095	18·285	84	34
LXVII.	2·72	5	10	3 hrs.	0	...	...	86	11·145	2·984	8·161	24·483	62	12
LXVIII.	2·72	5	10	4 hrs.	0·3	3	71	74	5·242	3·572	1·670	4·010	70	20

[1] The quantity of sulphate normally present in the fæces is not deducted. [2] Contents of stomach only. [3] Without solid fæces.

circulation. But the best observers state that purgation does not follow the intravenous injection of the salt, and in the next series of experiments I shall have reason to come to the same conclusion. We are, therefore, precluded from believing that it is the absorbed salt which, in the process of its after excretion, is the cause of the purgative secretion. The only alternative is, that the portion of the salt which causes purgation is that which remains within the alimentary canal, where, by its local stimulus of the glands, it is capable of effecting what it fails to do when passing with the blood through the glands. The absorption and excretion of the salt is a mere concurrent phenomenon which does not concern the essential action of the purgative. Nevertheless, it may be of great importance physiologically, and accordingly I have considered it worth while to determine as far as possible where and how it occurs. With this object I made the following two experiments, in which I ascertained that the rapid absorption of the salt in the early stage of its action does not take place in the stomach.

Experiment LXIX.—Cat, female, weighing 3·05 kilogrammes. Opened the abdomen by a short linear incision to the right of and close to the xiphoid cartilage, gently exposed the duodenum and pylorus, ligatured the latter, and afterwards the former below the entrance of the pancreatic and bile ducts, so that in the event of the secretions from the ducts being poured out they would collect between the pylorus and the ligature in the duodenum. The œsophagus in the neck was next exposed, carefully avoiding injury to the vagi and sympathetics, and two ligatures were placed round it, and an incision made into the tube between them. The upper ligature was applied to prevent the escape of saliva. The lower served to prevent the regurgitation of the saline solution after it had been injected into the stomach by means of a tube passing through the œsophageal incision. The stomach was previously ascertained to be empty by gently pressing it after the introduction of the empty tube. The cat, of course, had received no food or water for twenty hours before. 50 c.c. of a 10 per cent. solution of sulphate of soda (5 grammes of the salt) were Injected. Killed *one hour* afterwards.

Autopsy.—The stomach contained 55 c.c. of a colourless, slightly limpid fluid, faintly opalescent and of *alkaline* reaction. 10 c.c. required 0·14 c.c. of standard solution of oxalic acid for neutralisation. It contained the merest trace of albumen, but gave a dense white precipitate with nitrate of silver and nitric acid, showing that a quantity of chlorides was present. The whole of the fluid, along with the infusion of the stomach, yielded 4·510 grammes of

$Na_2SO_4.10H_2O$, reckoned, as usual, from the sulphuric acid recovered.

The duodenal loop was practically empty, containing only one or, at most, two drops of a very viscid bile. The whole of the remainder of the small intestine was perfectly empty, and was pale throughout. The colon contained a small quantity of firm fæces. The gall-bladder was well filled. The urinary bladder contained 8 c.c. of urine, and yielded sulphuric acid equivalent to 0·690 gramme of $Na_2SO_4.10H_2O$.

Experiment LXX.—Cat, female, weighing 2·27 kilogrammes. Operation conducted, and injection made, exactly as in the previous experiment, 50 c.c. of a 10 per cent. solution of sulphate of soda being injected. Killed after the lapse of *three hours and a half.*

Autopsy.—In the stomach were 69 c.c. of a perfectly colourless, limpid, faintly opalescent fluid, which filtered slowly; reaction, *alkaline*, 10 c.c. requiring 0·11 c.c. of standard solution of oxalic acid for neutralisation. The fluid contained a trace of glucose, and the faintest trace of albumen, when tested by the various reagents; no peptone reaction. It contained a large quantity of chlorides. There was little or no coagulation of mucin with excess of acetic acid. Acidified with hydrochloric acid, it digested fibrin with great facility.

The duodenal loop, as well as the remainder of the small intestine, was perfectly empty. In the upper third of the intestine was a number of irregular patches of congestion. The large intestine contained a small quantity of perfectly firm fæcal matter. Gall-bladder, distended with bile.

Half of the fluid from the stomach, with half the infusion of the stomach-wall, contained of sulphuric acid, estimated as $Na_2SO_4.10H_2O$, 2·042 grammes. The whole contents of the stomach, therefore, contained 4·084 grammes.

From these two experiments we learn that the absorption of the sulphate of soda takes place very slowly from the stomach of the cat, and that a 10 per cent. solution of the salt excites secretion in that organ with great difficulty. The rate of the absorption of the salt and of the increase of the saline fluid is very much less than was observed when the salt was administered *per os.* We cannot, therefore, but conclude that the stomach plays a subsidiary part in purgation, and contributes very little secretion when the solution administered is not stronger than 10 per cent., as is usually the case, although Experiment LXII. renders it probable that a 20 per cent. solution abstracts a fair amount of secretion.

A point of interest, both in these two experiments and in Experiment LXII., is the alkalinity of the gastric secretion. The acid-forming glands are apparently not capable of being stimu-

lated by the salt, although pepsin (Experiment LXX.) was not wanting in the secretion. The presence of pepsin in conjunction with a small amount of mucin would appear to indicate that the secretion is derived as much from the peptic follicles as from the mucous glands. The absence of congestion of the mucous membrane, and of albumen or its digested product, peptones, in the secretion, excludes the probability of the fluid being poured out as an inflammatory exudation from the superficial blood-vessels, without the intervention of the glands, which otherwise the alkalinity of the fluid might indicate, as such an exudation always possesses the alkaline reaction of the blood-serum. The determination of the exact nature of this secretion is of some importance; for it may help us to define the character of the copious secretion resulting from the action of the salt on the intestine. If the gastric secretion had been an ordinary acid gastric juice, we would have expected the intestinal secretion to be a true succus entericus. At least, the acid of the former is awanting, and it raises the possibility of the latter being likewise deficient in some of the constituents of the ordinary succus.

If, as we have just seen, the salt is not rapidly absorbed by the stomach, it appears almost superfluous to add experimental proof of its being much more quickly absorbed by the small intestine. For the rapid absorption in the early stage of the action of the salt must occur somewhere in the alimentary canal, and, if not in the stomach, then in the intestines, and, most probably, in the smaller of these. The next experiment will prove that such is the case.

Experiment LXXI.—Cat, male, weighing 2·75 kilogrammes. A short incision was made into the right hypochondrium, and the intestine exposed. Without withdrawing more than an inch or two of the gut, the small intestine was ligatured at the pylorus and close to the cœcum. As both ends of the intestine lay almost immediately beneath the seat of the incision, there was no unnecessary disturbance of the abdominal viscera. As the cat had not received food for nearly twenty-six hours previously, it was certain that the intestine was empty. Through a small incision in the upper end of the duodenum, afterwards ligatured off, 50 c.c. of a 10 per cent. solution of sulphate of soda (5 grammes of the salt) were injected into the small intestine. Killed *three hours, thirty-five minutes* afterwards.

AUTOPSY.—The small intestine was moderately distended with

106 c.c. of a slightly brown, otherwise transparent, fluid; it was somewhat viscid, and contained a few shreddy remnants of food, and whitish flakes. Its reaction was alkaline. There was no yellow tint in the colour of the fluid, and no perceptible bile reaction with the usual reagents.

The stomach was perfectly empty, and the colon contained a quantity of the usual firm fæces, but *not a drop of fluid.*

The mucous membrane of the intestines was pale and uncongested in its whole extent, with the exception of a few centimetres near the pylorus, which showed evidence of a limited chronic congestion.

The fluid from the small intestine yielded, along with the infusion, 2·753 grammes of $Na_2SO_4 \cdot 10H_2O$, as calculated from the sulphuric acid recovered. Half of the fluid and infusion was used for this purpose, the other half of the fluid being reserved for ascertaining its digestive power. 5 c.c. mixed with 10 c.c. of a 1 per cent. solution of starch and placed in the digesting-oven, reduced Fehling after 35 minutes' digestion. The same quantity of the fluid added to 10 c.c. of a 1 per cent. solution of cane-sugar showed the first trace of invert-sugar after one hour, forty-five minutes.

From the comparatively slow digestion of the starch, it is evident that the fluid contained very little pancreatic juice. As the salt solution was injected, and the last ligature applied above the entrance of the bile and pancreatic ducts, the absence of bile, as ascertained by the want of colour in the fluid and the application of reagents, and the absence of pancreatic juice, as discovered from the weak diastatic power of the fluid, confirm the conclusion arrived at from previous experiments, that these secretions do not to any extent form a part of the purgative fluid.

The main result of this experiment is as was anticipated. The absorption of the salt, and the secretion of fluid, are much more rapid in the small intestine than in the stomach; and we may assume that it is in the former these processes chiefly take place when the salt is administered *per os.*

These last three experiments will help us to explain the results obtained from the experiments which preceded them. I have already given one sufficent reason[1] for discrediting Headland's theory of the action of the purgative salt; and to this I have now to add the fact, proved by these experiments, that the absorbed salt never appears accompanied by secretion in a portion of the alimentary canal lower than that into which

[1] P. 105.

it has been injected. A small quantity of salt is absorbed by the stomach, but none of it and no fluid are found, even after more than three hours, in the intestines. A much larger quantity is absorbed by the small intestine, yet none of it reappears in the large intestine, and not a drop of fluid is secreted by that viscus. And I think we may safely take it for granted that, had the salt injected been confined to the upper half of the small intestine, neither salt nor fluid would have been found in the lower half. So that, neither when the salt is directly injected into the blood—the proof of this I have yet to offer—nor when absorbed from the alimentary canal, is it capable of exciting secretion in any alimentary gland through whose vessels it circulates. Local, or, if we might say so, external, contact of the salt and the gland is essential for the stimulation of the latter. Headland adduces in support of his theory Carpenter's [1] single experiment, in which the latter saw purgation follow the injection of sulphate of magnesia into the stomach of a dog with its pylorus ligatured. This is quite opposed to my two experiments, and, as purgation only followed after a considerable time in Carpenter's experiment, it was doubtless due to the mere irritation of the intestines produced by the operation. Carpenter does not appear to have examined the dejection for the salt.

Considering it as fully proved that it is the salt remaining within the alimentary canal which stimulates the glands and purges, we can understand how a quantity of a saline purgative short of a full dose is so little apt to produce a laxative effect commensurate with the quantity of the salt administered, as is the case with most of the vegetable cathartics. A saline purgative, as a rule, either causes a free watery stool or entirely fails to act. If the dose administered be such as not to exceed what can be absorbed from the canal during the stage of rapid absorption, then too little remains within the canal to excite the glands to secretion, and purgation does not occur. On the contrary, constipation is more likely to follow from the diuretic action of the absorbed salt depriving the body of its usual quantity of fluids.

But we have yet to explain how the salt begins to reappear

[1] Carpenter, *op. cit.*

in the canal after its absorption. This cumulative excretion of the salt does not probably occur in the locus of its absorption; for we cannot understand how the same mucous membrane should first quickly absorb the salt, afterwards as quickly excrete it, and, finally, slowly absorb it. The increase of the salt cannot, therefore, well take place in the small intestine, where we believe absorption mainly happens. And this supposition receives support from the last experiment, in which the quantity of the recovered salt was such as to indicate that absorption had not been followed by excretion. We are, accordingly, forced to conclude that the salt gains in quantity after the saline fluid has reached the large intestine, and that this is dependent on a difference in the structure and function of the large intestine as compared with the small intestine. If a solution of a salt be injected into the small intestine, the rapidity of the disappearance of the salt will depend on two factors, absorption and secretion. We have reason to believe, from the B. Series of Experiments, that, however dilute the saline solution may be, and whatever change it may undergo in bulk, both processes of absorption and secretion are very active; and it is reasonable to suppose that their activity will finally lead to an equal proportion or percentage of the salt in the blood and in the fluid within the intestine. This will certainly happen, if the fluid absorbed contain the same proportion of the salt as the intestinal fluid from which it is drawn, and if the fluid secreted contains the same proportion of the salt as the blood. The proportion of salt in the absorbed fluid will gradually grow less, whilst its proportion in the secreted fluid will gradually increase, until both are equal, when the blood and intestinal fluid will contain a like percentage of the salt, and the absolute quantity of the salt in each will be respectively as their bulks. If this be so, then, after the administration of a solution of 5 grammes of sulphate of soda to a cat weighing about 3 kilogrammes, a dose which we know from experiment to increase the fluid within the alimentary canal to about 100 c.c., we would expect to find in the blood two-thirds, and in the intestinal fluid one-third, of the salt given, reckoning that one-fifteenth part of the weight of the cat, or 200 grammes, is blood. But in none of the experiments recorded is the minimum of salt within the canal so low

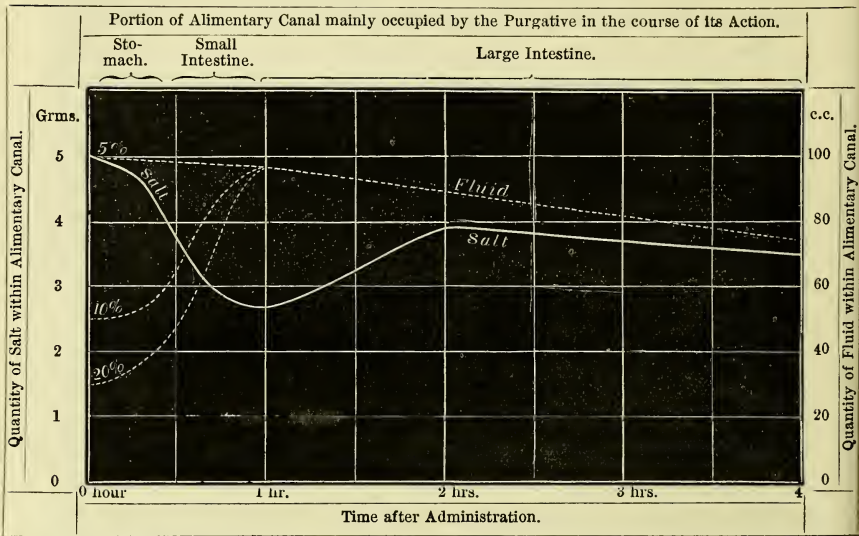
as one-third, not even in Experiment LXXI., where the salt was permitted to remain for some hours in the intestine, and where ample time was allowed for the blood being recouped by the tissue-fluids for what serum it may have yielded to the intestine. Therefore, either the secretion excited by the salt contains a larger proportion of the salt than the blood, or the absorbed fluid contains a less proportion than the fluid within the intestine. The former alternative is improbable; for no secretion, physiological or pathological, in the body contains a higher percentage of salts than the blood from which it is derived. The urine is a notable exception; but according to Ludwig's well-known theory, the excess of the salts is explained by the absorption in the tubuli uriniferi of a portion of the water of the glomerular secretion. The latter alternative is not without probability. The villi of the intestine may exercise a certain power of selection in absorption, and absorb from a saline solution more of the water and less of the salt than the proportion in which they exist in the solution. This supposition is rendered possible by what we know of the absorption of saline solutions by the roots of plants,[1] and it is supported by experiments on the imbibition of saline solutions by animal tissues. Ludwig[2] observed that a piece of dried urinary bladder, placed in a 7·2 per cent. solution of sulphate of soda, became saturated with a fluid containing only 4·4 per cent. of the salt. Indeed, absorption seems, for the most part, to be governed by the laws which regulate imbibition and diffusion, secretion by the laws of filtration.

If the small intestine exhibit in its absorption of a solution of sulphate of soda a preference for the water, we have only to believe, in order to understand the rapid accumulation of the salt within the alimentary canal during the second hour of the action of the salt, that the preference for the water and the rejection of the salt are manifested to a still greater degree in the absorptive function of the large intestine. So that, when the saline fluid passes into the colon, a secretion with the same percentage of the salt as the blood will be poured out, just as it was in the small intestine; but in the absorbed fluid the

[1] Saussure, *Recherch. chemiq. sur la végétat.*

[2] Ludwig, *Lehrbuch der Physiologie*, Bd. i. s. 54 *et seq.*

percentage of the salt will be much less than in the intestinal fluid, and still less than that in the fluid absorbed by the small intestine. The salt will thus quickly accumulate within the colon.



Graphic Representation of the Course of the Variations in the Quantity of Salt and Fluid within the Alimentary Canal after the administration of a 5, 10, or 20 per cent. solution of 5 grms. of Crystalline Sulphate of Soda to a Cat. The salt is calculated from the sulphuric acid recovered.

In this way it is possible to offer an explanation of a phenomenon, or a series of phenomena, otherwise very difficult to comprehend. In accordance with this view I have prepared a diagram which shows the variations of the salt in its passage through the alimentary canal, and which attempts to define in what portion of the canal each of the variations occur.

Series of Experiments, E.

On the effect of the salt when injected into the blood

Considering the large and weighty array of investigators who have affirmed that the intravenous injection of a saline purgative is not followed by its usual cathartic action, it seems almost unnecessary that I should have made further experiments to determine the accuracy of this statement. Amongst others,

however, such skilled observers as Claude Bernard, Aubert, and Headland[1] have stated that the salt produces purgation as efficiently when injected into the blood as when administered in the usual manner. Having regard to the great importance of this fact in its bearing on the interpretation of the phenomena observed in the preceding series of experiments, I felt justified in ascertaining its truth for myself.

Buchheim and Wagner, Donders, and Vulpian maintain, from a considerable number of experiments, that the sulphate of soda never purges when injected intravenously, but tends, on the contrary, to produce constipation. Bernard, Headland, and Aubert seem to have employed the same salt, and obtained, as I have just mentioned, an opposite result. Their experiments were few in number. Aubert made the experiment but once, and Bernard and Headland do not give an account of their experiments, and leave it, indeed, doubtful whether they themselves actually made such experiments. Jolyet and Cahours have injected into the circulation of two different dogs sulphate of soda and sulphate of magnesia, and, although the latter was followed by two diarrhœac evacuations in the course of the succeeding night, these observers, believing that purgation was exceptional, and might ensue from some other cause than the injection of the salt, are strongly inclined to maintain that the salt does not purge when so injected. Aguilhon has recently stated that catharsis always follows the intravenous injection of the chloride of magnesium. This, however, is denied by Rabuteau, who has injected the sulphate as well as the chloride of magnesium without perceiving any effect on the intestines. Paul Bert,[2] in criticising a communication by Laborde to the Société de Biologie on the stimulant action of the chloride on the intestines when injected into the blood, said that he himself had made a few experiments with the sulphate without ever having perceived purgation occur ; and Bordier,[3] in a review of the papers of Luton and Vulpian, cites Moreau as having obtained the same negative result.

While there is thus little doubt, from the large number of

[1] References for these and the others are given in the historical introduction.

[2] Bert, *Gaz. hebdom.*, 1879, p. 366.

[3] Bordier, *Journ. de Pharmacie*, t. xx. p. 132.

authenticated experiments, that the sulphate of soda is inactive as a purgative when introduced into the circulation, and while the preponderance of evidence is in favour of a salt of magnesia being equally devoid of purgation when similarly injected, it is still desirable to learn with yet greater precision what are the actual effects of these salts when so injected, particularly of the latter, as being the more doubtful.

Experiment LXXII.—Rabbit, male, weighing 1·58 kilogrammes. No anæsthetic was administered. In order to render the condition of the alimentary canal as favourable as possible for the production of purgation, the experiment was commenced by the injection *per os* of 90 c.c. of water into the stomach. Quarter of an hour afterwards I began the injection into the right external jugular vein of a 10 per cent. solution of sulphate of soda. The solution was placed in a Mohr's burette connected with the vein, and by means of a stop-cock the flow was so regulated as to be slow, uniform, and continuous. In fifty-five minutes the injection was completed, 50 c.c. of the solution or 5 grammes of the salt having been introduced. Immediately afterwards the rabbit was released from the holder, and, although it appeared a little weak and ate no food during the remainder of the day, did not otherwise suffer from the experiment. One hour after the completion of the operation water to the extent of 60 c.c. was again injected into the stomach.

On the following day the rabbit had quite recovered from the effects of the operation. As yet there was no evacuation of fæces, nor did such occur until four days after the injection of the salt, when only a few pellets of hard fæces were passed.

A dose, therefore, of sulphate of soda, which in previous experiments was found amply sufficient to cause purgation when administered *per os* to a rabbit of average size, has failed to produce this effect when injected into the circulation, and that even with the alimentary canal in a condition most favourable for catharsis. On the contrary, a considerable degree of constipation seems to have followed. The salt was slowly injected with the object of imitating, as far as possible, the rate of absorption of the salt when administered in the ordinary manner. For had the whole of the salt been at once introduced into the circulation, the greater part of it might have been eliminated by the kidneys before it had sufficient time to produce its characteristic action on the intestine.

Experiment LXXIII.—Cat, female, weighing 1·81 kilogrammes. Received no solid food for one day previous to the experiment. An-

æsthetised with a mixture of chloroform and ether. At first a 5 per cent. and later a 10 per cent. solution of sulphate of soda was injected by means of an ordinary syringe and cannula into the saphenous vein of the right hind leg. The injection was commenced at 5.7½ P.M., the cannula having been inserted at 4.45 P.M.

Time.	Quantity of Salt Solution injected.	Pulse per Minute.	Respirations per Minute.
5.5 P.M.	...	112	28
5.7½ to 5.10	3 c.c.	...	...
5.14	...	112	26
5.15 to 5.20	7 c.c.	...	...
5.24	...	112	28
5.25 to 5.30	10 c.c.	...	...
5.35	...	122	20
The strength of	the solution was	now increased to	10 per cent.
5.36 to 5.40	4 c.c.	...	...
5.45	...	124	22
5.46 to 5.50	6 c.c.	...	...
5.54	...	128	24
5.55	5 c.c.	...	...
5.59	...	136	20
6.3	5 c.c.	...	...
6.10	...	148	24
6.13	5 c.c.	...	...
6.17	...	136	20
6.20	5 c.c.	...	...
6.24	...	132	22
6.26	5 c.c.	...	...
6.30	...	132	20
6.32	5 c.c.	...	...
6.40	...	128	20

Five grammes of the sulphate having been injected, the cannula was removed from the vein, and the cat was allowed to recover from the anæsthetic which had been administered as lightly as possible.

At 7.20 P.M. it looked dull, but was perfectly conscious: pulse, 126; respirations, 22. It was now released from the holder, when it walked slowly in a somewhat cramped fashion.

At 7.45 P.M. it was reattached to the holder and anæsthetised, and the abdomen opened for the purpose of observing the viscera. There were no movements of any portion of the intestines, and no visible congestion. Quarter of an hour afterwards it was killed with excess of the anæsthetic.

Autopsy.—The stomach contained 2 c.c. of a clear alkaline fluid smelling of chloroform, and yielding a distinct but not very abundant precipitate with barium chloride and hydrochloric acid, proving the presence of a trace of sulphates. The small intestine, 147 cm. in length contained three drops of a brown thickish fluid; the mucous membrane in its whole extent was perfectly pale. The colon was

filled with the usual firm fæcal matter, which was ascertained to contain 66·1 per cent. of water, or the normal proportion; its mucous membrane was also pale. The gall-bladder was tolerably distended with bile. The urine measured 56 c.c., and contained sugar, of which the whole urine was estimated by Pavy's method to contain 0·958 grammes. The urine was acid, each 10 c.c. having an acidity corresponding to 0·30 c.c. of the pharmacopœial standard solution of oxalic acid. From an analysis of half of the original quantity of the urine, the whole was estimated to contain 2·846 grammes of crystalline sulphate of soda. How much urine there was in the bladder previous to beginning the experiment I had no means of knowing, but I have reason to believe there was not much, so that the sulphate recovered was not greatly increased by the normal excretion of sulphuric acid.

The result of this experiment is highly interesting. For it shows that if the condition of the alimentary canal be observed a few hours after the intravenous injection of a purgative dose of sulphate of soda, it does not present the slightest evidence of purgative action. The canal was virtually empty, and contained a trace only of sulphates; the mucous membrane of the entire tract did not exhibit the smallest degree of congestion, and there was no visible excitement of the peristalsis.

Not much importance can be attached to small variations in the rate of the pulse and the respirations of an anæsthetised animal, but, as during the experiment the anæsthetic was as equally administered as possible, the increased pulse-rate observed and the diminished frequency of the respirations may be regarded as the effect of the injected salt. The rate of the pulse, it will be noticed, did not continue to increase, but began to fall towards the end of the experiment.

Another experiment, made in the same manner as the preceding, and whose abbreviated protocol I add, shows that, if the cat be allowed to live for some days after the injection of the salt, the tendency is, as with the rabbit, towards constipation rather than purgation.

Experiment LXXIV.—Cat, male, weighing 2·03 kilogrammes. Fed eighteen hours previously. In the forenoon, and in the course of one hour, 60 c.c. of a 10 per cent. solution of sulphate of soda, or 6 grammes of the salt, were injected into the saphenous vein of the left hind leg, 5 c.c. being injected every five minutes.

Neither during the day of the operation nor on the following day were there any fæces evacuated. On the third evening there was a small quantity of hard fæces.

The urine collected during the first twenty-four hours gave a distinct sugar reaction, but contained no albumen.

In conjunction with the results of previous observers we are perfectly warranted in concluding from these three experiments that the sulphate of soda is quite incapable of inducing its usual purgative effect when injected into the circulation. On the contrary, a degree of constipation appears usually to follow.

A somewhat remarkable phenomenon observed in the course of these and similar experiments is the appearance of sugar (glucose presumably) in the urine. On referring to Hermann's *Physiology*, I find that Bock and Hoffmann are credited with the statement that very dilute saline solutions cause, when injected into the blood, a temporary diabetes mellitus. I have more than once observed the same result follow the injection of the salt into a ligatured loop of intestine. It is not improbable that the salt in the blood may hinder the assimilation of the carbo-hydrate by the tissues, while its production in the liver proceeding as usual may lead to its accumulation in the blood and its discharge in the renal secretion.

Sulphate of magnesia was employed in the next experiments, the main interest of which lies in their proof of the high toxic power possessed by this salt as compared with the corresponding salt of soda. This toxicity is but very vaguely understood and not generally known, scarcely one of the best text-books on pharmacology alluding to it with emphasis.

Experiment LXXV.—Dog, weighing 7·25 kilogrammes. Anæsthetised. During the injection of a 20 per cent. solution of sulphate of magnesia into the external saphenous vein of the left hind leg, and when not more than 3 c.c. had been injected, the animal died, and animation could not be restored by means of artificial respiration. Death may have resulted from an over-dose of the anæsthetic, but this is improbable. It was more likely due to the sudden injection of the concentrated solution of the salt, for death immediately followed the injection. The quantity of the salt—0·6 gramme—was extremely small, and was not more than the twentieth part of a purgative dose.

Not being aware, as yet, of the high toxic power of this salt, I attributed the death of the dog to the anæsthetic, and proceeded to repeat the experiment on a cat.

Experiment LXXVI.—Cat, female, weighing 2·28 kilogrammes.

[1] Hermann's *Elements of Physiology*, translated by Gamgee, 1875, p. 189.

Lightly anæsthetised. Not more than 1·5 c.c. of a 20 per cent. solution of sulphate of magnesia had been leisurely injected into the saphenous vein, when the cat died as suddenly as the dog had done.

As I now suspected that the sudden and fatal termination of these two experiments was due to the salt, I took another cat, and injected a 10 per cent. solution very slowly and cautiously, so as to obviate as far as possible the directly and locally paralytic effect of the salt on the heart from possible irritation of the endocardium. I need hardly state that I ascertained that the salt used was chemically pure.

Experiment LXXVI.—Cat, female, weighing 2·26 kilogrammes. A 10 per cent. solution of sulphate of magnesia was injected into the left external saphenous vein, and injected so slowly that twenty minutes were occupied in introducing 6 c.c. When this point had been reached respiration altogether ceased, while the heart continued to beat, although with greatly diminished rapidity. Sylvester's method of artificial respiration was maintained for a few minutes, until natural respiration recommenced. On account of the animal having appeared perfectly unconscious since a few minutes after the commencement of the injection of the salt, no anæsthetic had from that time been applied. During the forty minutes succeeding the recovery of the animal from suspended respiration 7 c.c. of the saline solution were gradually injected. This was followed once more by cessation of respiration, the heart beating irregularly at the rate of 31 per minute. Previous to the experiment it was 146. Artificial respiration was at once resorted to, and maintained for ten minutes, but ineffectually. The heart meanwhile was beating very slowly, and gradually becoming weaker until it finally stopped, without a single effort having been made by the animal to respire.

Autopsy.—The abdomen was immediately opened, and the intestines observed to be quite at rest, and perfectly empty, with the exception of the colon, which contained the usual semi-solid fæces. The mucous membrane of the canal was pale, unless for 20 cm. below the pylorus, where there existed small irregular and moderately congested patches, evidently of a chronic character. There were no tapeworms. The urine did not contain much magnesia.

This experiment rendered it perfectly clear that sulphate of magnesia possessed considerable toxic power; and from the care employed in its injection it was highly probable that the amount of the salt used—1·3 grammes—was the lethal dose for a cat weighing 2·26 kilogrammes. This quantity is much larger than that needed in the two previous experiments, but in these it is almost certain that the greater concentration of the saline

solution and its more rapid injection directly affected the heart and respiration.

Having now ascertained the lethal dose of sulphate of magnesia, which, it will be observed, is far short of the dose required *per os* for purgation, I proceeded to inject into the circulation of another cat as much of the salt as I possibly could short of causing death, with the object of learning if purgation might follow.

Experiment LXXVII.—Cat, female, weighing 1·81 kilogrammes. Anæsthetised. A 5 per cent. solution of sulphate of magnesia was injected into the external saphenous vein of the left hind leg.

Time.	Quantity of Salt Solution injected.	Pulse per Minute.	Respirations per Minute.
4.10 P.M.	...	128	56
4.15 to 4.16	2 c.c.	...	...
4.20 [1]	...	140	32
4.21 to 4.32	6 c.c.	...	...
4.35 [2]	...	108	26
4.36 to 4.38	2 c.c.	...	...
4.41	...	104	24
4.42 to 4.47	2·5 c.c.	...	...
4.50	...	84	20
4.51 to 4.57	2·5 c.c.	...	...
5	...	76	18
5.1 to 5.7 [3]	5 c.c.	...	...
5.10	...	76	17
5.12	1 c.c.	...	...
5.13	...	40–52 irregular.	very slow and deep.
5.13½	2 c.c.		

5.14.—Respiration ceased, followed infifteen seconds by the stoppage of the heart. Sylvestrian artificial respiration was at once practised, and one minute afterwards the heart commenced to beat, but very slowly. Four minutes later, natural respiration returned, and artificial respiration was stopped.

5.24.—Again stoppage of the respiration, followed by that of the heart. Artificial respiration was once more resorted to.

[1] The application of the anæsthetic was discontinued, as the animal remained unconscious without it.

[2] From this time the conjunctivæ were quite insensible to stimuli, nor could pinching of any part of the body provoke a reflex movement. The animal appeared to be in a state of profound narcosis.

[3] At 5.4 there was a gentle movement of the whole body, and slight reflex sensibility of the conjunctivæ.

5.26.—The heart's action restored, and four minutes afterwards the pulse was 40.

5.37.—Artificial respiration stopped; and, although the heart continued to beat, it was not until three or four minutes afterwards that natural respiration attempted to reassert itself by an occasional upheaval of the upper part of the chest, the diaphragm remaining apparently quite inactive. Respiration was gradually established. Reflex sensibility of every part of the body still completely abolished.

5.43.—Pulse 42, and respirations 8.

5.48.—Pulse 48, and respirations 10.

The wound was now closed, and the cat was removed from the holder. It was still perfectly insensible to stimulation. The pupils contracted very slowly on exposure to light, and, when contracted, their dilatation in the dark occupied several minutes, an operation accomplished almost momentarily in the normal cat.

5.55.—Pulse 48, and respirations 12. Three minutes later the cat made a few feeble and very limited spontaneous movements.

6.5—Constant small twitching movements of all the limbs commenced. Conjunctivæ still insensible. Pulse now 64, and respirations 18.

6.25.—The twitchings had ceased, and there were instead occasional movements of the head.

6.45.—Pulse 80, and respirations 22 ; conjunctivæ not yet sensible.

7.5.—Pulse 102, and respirations 32. Conjunctivæ had now become slightly sensible, and the animal made fair co-ordinate efforts to move.

8.0—Pulse 104, and respirations 24 ; able to sit up, but very weak. Conjunctivæ quite sensible.

9.0.—Pulse 104, respirations 24; still very helpless, although a little stronger.

Next day it looked as well and as lively as it did before the experiment, and enjoyed its food. Pulse 192, respirations 48 to 56. It appeared to be very thirsty during the day. No fæces passed as yet.

On the third day there was a small evacuation of hard fæces in the afternoon.

Altogether, 23 c.c. of the salt solution, or 1·15 grammes of the salt, were injected.

This experiment fully warrants the deduction that sulphate of magnesia, no more than sulphate of soda, is capable of purging when injected intravenously. There is, however, this important difference, that whereas a full purgative dose of the latter salt can be introduced with impunity into the circulation, not more than one-fifth part of an ordinary dose of the former can be injected without endangering the life of the animal. And it is possible that, could more of the sulphate of magnesia be introduced into the blood, it might affect the intestines, and produce

catharsis. But this is in the highest degree improbable, as in Experiment LXXVI., where the animal died some time after the injection of the salt, not the least sign of cathartic action was visible in the intestines.

If it be admitted, then, that a saline cathartic does not produce its characteristic action when injected into the blood, we have proved a fact which is not at variance with the results of the previous series of experiments, or with the theories I have attempted to base upon them. We are, therefore, now entitled to dismiss Headland's theory, that it is the salt which is absorbed by the blood that causes purgation in the course of its excretion by the intestinal glands. We cannot, however, so easily rid ourselves of the results of the experiments upon which, in part, his theory was grounded. It will be remembered, that in these experiments Headland administered 180 grains (about $11\frac{1}{2}$ grammes) of sulphate of magnesia to each of three dogs, and that from the alimentary canal of one of the animals he recovered less than one-third of the salt; so that about $7\frac{1}{2}$ grammes had evidently been absorbed by the blood. The question naturally arises, if this be so, why were none of the toxic symptoms of the magnesia salt witnessed in the animals to which it had been administered; and why, indeed, were none of these symptoms observable in the various animals to which in the course of this investigation I gave large doses of the salt? The absence of such symptoms might be held as proof that no such absorption had occurred; or it might be suggested that dogs, the only animals used by Headland, are not amenable to the poisonous action of magnesia. But, that such an absorption did occur, is placed almost beyond doubt by my more numerous experiments on cats with the sulphate of soda (Series D.), in which it was observed that more than $2\frac{1}{2}$ grammes, or the half of the salt administered, had disappeared within the first hour from the alimentary canal. Nor, apart from the improbability of the suggestion, are dogs less susceptible than cats of the toxic action of magnesia; for, excluding my single experiment in which a dog died after the injection of 0·6 gramme of the sulphate, Jolyet and Cahours[1] seriously imperilled the life of a dog by injecting into its circulation 6 grammes of the same salt.

[1] *Op. cit.*

Yet $7\frac{1}{2}$ grammes must have been absorbed in Headland's experiment without the slightest symptom of poisoning. In reconciling the results of the experiments of this series and of those of the preceding series, we have to face a difficulty of considerable magnitude. Sulphate of magnesia produces well-marked symptoms when directly injected, even in very small quantity, into the blood. Yet the same salt, when absorbed from the alimentary canal, and in comparatively large quantity, causes no general symptoms whatever. Either the salt which disappears from the canal does not enter the blood, or it enters the blood in such a form or chemical combination that it is no longer capable of affecting the activity of the tissues and organs with which it comes in contact. Analyses of the blood are, as yet, wanting to test the probability of the latter supposition; these I hope ere long to supply. Should the former alternative prove true, a still greater difficulty presents itself, when we come to consider by what channel, or into what organ, the salt has disappeared. In so far as our present knowledge of anatomy and physiology can help us, we can only think of its being absorbed by the liver from the blood of the portal vein, and restored to the intestines through the medium of the biliary secretion; for, both according to Headland's experiments and to mine, the salt after its first rapid absorption returns to the alimentary canal. But my observations have led me to conclude that the bile takes little or no part in the formation of the fluid of saline catharsis; in D. Series of Experiments a mere tinging of the intestinal contents with bile was of rare occurrence. On the other hand, the recent researches of Héger and Jacque[1] have proved that the liver is capable of absorbing a large proportion of certain alkaloids, when injected into the mesenteric vein, as much as 25 to 50 per cent. of nicotin having been absorbed in this manner. Their elimination in the bile they have not quite so satisfactorily demonstrated. On the whole, I prefer to express the opinion, that whatever be the circuit traversed by the salt after leaving the alimentary canal, it is not through the liver and gall-bladder. The solution of this difficulty requires further research.

[1] Héger et Jacque, *Gazette hebdom.*, No. 29, 1880.

Apart from the bearing of these experiments with sulphate of magnesia on the nature of the purgative action of the salt, they are of interest as tracing with some precision the effect of the salt on the circulation and respiration when injected into the blood. The pulse is at first slightly accelerated, but soon begins to diminish in rapidity until, following the stoppage of the respiration, it ceases to be felt. The respirations are from the first lessened in frequency, and it is to the paralysis of their motor centre that death is to be attributed. The action of the salt on the respiratory centre is not, however, permanent; for, if artificial respiration be maintained for a few minutes, until the excess of the salt has been eliminated from the blood, or otherwise rendered less active, natural respiration will reassert itself, although with greatly enfeebled activity. The fact of the heart continuing to beat throughout the maintenance of the artificial respiration, and while natural respiration remains as yet paralysed, points to the salt acting more powerfully on the respiration than on the heart. A remarkable feature is the abolition of reflex sensibility, which is complete within twenty minutes after the commencement of the injection, and when not more than 0·4 gramme of the salt has been administered, and which continues for one hour and a half after the paralysed respiration has been re-established, and for more than one hour and three quarters after the injection of the salt has been completed. This affection of the reflex sensibility seems to depend upon paralysis of the sensory nerves, or of the reflex centres, not upon paralysis of the motor nerves or the muscles. For voluntary movements of the body are visible long before reflex sensibility has been restored. Altogether the action of magnesia is remarkable, and precludes its being classed with any recognised metallic pharmacological group.

Without taking into consideration the more puzzling points which I have already endeavoured to elucidate, it may appear somewhat surprising that so large a dose of sulphate of magnesia can be administered by the mouth with absolute safety, whilst a fraction of this dose is sufficient to produce the serious symptoms I have described, and even death, when injected directly into the blood. This pharmacological paradox is not singular; for, not to speak of the well-known instance of curara, the salts of potash

show a similar behaviour. The potash salts are, when injected into the blood, nearly four or five times as poisonous as the magnesia salts;[1] yet an ounce of the sulphate of potash may be swallowed by a man, or 8 to 10 grammes administered to a cat, without causing more than free purgation. The explanation hitherto given has been that, owing to the elimination of the substance by the kidney being as rapid as its absorption from the alimentary viscera, it does not accumulate in the blood in quantity sufficient to produce its general toxic symptoms. Accepting as accurate the results of Headland's and my experiments, this explanation is obviously not applicable to the salts of magnesia; and as little may it be the true explanation of the behaviour of the potash salts.

Amidst much that is uncertain, there is but one sure conclusion that can be inferred from these experiments in conjunction with those of the various preceding series—that it is not the absorbed salt which causes purgation by stimulation of the intestinal glands in the process of its excretion, but it is the salt remaining within the intestines which excites the glands; and the reappearance of the salt in the intestines is not the cause of the secretion, but merely the accompaniment of it.

In the following experiment an artificial imitation was attempted of the supposed relative distribution of the sulphate of soda in the blood and alimentary canal one hour after the administration of a purgative dose *per os*, with the object of ascertaining if, under these circumstances, purgation would follow.

Experiment LXXVIII.—Black cat, female, weighing 3·02 kilogrammes. 25 c.c. of a 10 per cent. solution of sulphate of soda, or $2\frac{1}{2}$ grammes of the salt, were first administered in the ordinary manner, to observe if this quantity of itself was sufficient to purge. No purgation followed. Three days afterwards, 3 grammes of the salt (20 per cent. solution) were injected into the external saphenous vein of the left hind leg. The injection extended over ten minutes, and the animal was anæsthetised. Immediately afterwards, it was released from the holder, and $2\frac{1}{2}$ grammes of the salt (10 per cent. solution) were injected *per os* into the stomach. Purgation never occurred, although the animal was observed for two days afterwards.

The artificial distribution of the salt in the blood and the alimentary canal was not, therefore, followed by purgation, as I

[1] Mickwitz found that the intravenous injection of 0·2 gramme of nitrate of potash killed a cat.—*Nothnagel u. Rossbach's Arzneimittellehre*, 1878, s. 14.

had partly anticipated. On a point like this a single experiment is not conclusive. But, supposing that the result is exactly as it should be, then I either failed to imitate exactly the condition of the salt, when all of it had been administered by the mouth, or some factors came into operation in this experiment which might have interfered with the effect of the salt. As regards the latter, the cat took almost no food and very little water for two days previous to the experiment, and this may have led to concentration of the blood, a condition which I have proved to interfere materially with the purgative action of the salt. As concerns the former, I failed to imitate perfectly the condition of the salt in one important respect, inasmuch as the portion of the salt administered by the mouth was at the upper end of the alimentary canal, and not at its lower end, as is the case one hour after the administration of the whole dose of the salt by the mouth, and it had to traverse the length of the highly absorptive small intestine, where possibly so much of it was absorbed by the blood that too little remained in the intestines to stimulate sufficiently the enteric glands. The incorrectness of the imitation may have been still more gross. For there is the possibility, previously alluded to, that the salt which disappears from the canal may not be found in the systemic circulation. In such a case a negative result was quite to be expected.

TABULATED SUMMARY OF THE EXPERIMENTS OF SERIES D.

Number of Experiment.	Animal.	Weight of Animal.	Salt employed.	Quantity of Salt injected.	Remarks.
		kilogrms.		grms.	
LXXII.	Rabbit	1·58	Sulphate of soda	5	150 c.c. of water injected *per os*: constipation.
LXXIII.	Cat	1·81	,,	5	Afterwards killed: no signs of purgation.
LXXIV.	,,	2·03	,,	6	Constipation.
LXXV.	Dog	7·25	Sulphate of magnesia	0·6	Died suddenly.
LXXVI.	Cat	2·26	,,	1·3	Died after one hour: no signs of purgation.
LXXVII.	,,	1·81	,,	1·15	Constipation.
LXXVIII.	,,	3·02	Sulphate of soda	3	3 grms. also given *per os*: no purgation.

Series of Experiments, F.

On the purgative effect of the salt when injected subcutaneously.

After the tolerably exhaustive inquiry which I have made into the action of the salt when directly introduced into the circulation, it may appear superfluous to investigate the effect of the salt when injected subcutaneously. For, whether a soluble salt be injected into a vein or beneath the skin, the belief is that it produces its peculiar action, if not equally quickly, at least as equally powerfully, the salt passing rapidly, in the latter case, from the subcutaneous tissue into the circulation. It was, therefore, to be expected that the action of the salt would be the same in both cases. And so it was believed, until Luton, an eminent physician of Reims, accidentally observed that one decigramme ($1\frac{1}{2}$ grains) of sulphate of magnesia could produce purgation when injected subcutaneously. I have not had an opportunity of consulting the *Bulletin de la Soc. Méd. de Reims*, in which his communication appeared, but have seen, what I take to be, a fairly complete *résumé* of it in the *Gazette hebdomadaire* (1874, p. 455). Four experiments were altogether made, and all of them on man, and in each instance free purgation followed. Unfortunately, the situation of the injection is not mentioned, but I presume it was made beneath the skin of the abdomen, the situation chosen by Vulpian and Carville,[1] when, a few months later, they repeated with the same result these experiments on dogs. The original communication of Luton is, as the editor of the *Gazette hebdomadaire* remarks, silent as to the production of pain at the seat of injection. In Vulpian and Carville's experiments a considerable degree of pain and inflammatory swelling followed; and it is not improbable that this was also observed by Luton, although not recorded. In attempting to explain the powerful action of so remarkably small a dose of sulphate of magnesia, Vulpian believes that the salt is absorbed and effects catharsis by its action on some portion of the intestinal or alimentary mechanism. But it is certainly surprising that, when the same salt is injected into the blood, purgation does not follow. And Vulpian, as he

[1] Vulpian, *Leçons sur l'appareil vasomoteur*, t. i. p. 515 ; Carville, *Gaz. hebdom.*, 1874, p. 405; *et supra*, p. 8.

himself admits, injected directly into the circulation both large and minute doses of sulphate of soda without producing any effect. In spite of these considerations Vulpian, in common with Luton and Carville, adheres to the view he originally advanced.

The activity ascribed to the absorption of an almost infinitesimal dose of sulphate of magnesia seemed so incredible that Gubler attributed the purgative effect in the case of man, not to the injection of the salt, but to the mere anticipation of such a result, the individual having been informed that purgation was expected. This, in the less scientific and cultivated minds of the inmates of an hospital, where as yet all the experiments on man had been made, Gubler[1] considered very likely to occur. To test the truth of his supposition, he administered the salt in the same manner to a large number of the students attending his clinique, upon whom the moral effect of the injection was reduced to a minimum. The result was highly favourable to his theory. For only in a very small percentage of those submitted to the action of the salt did purgation occur. The seat of the injection appears to have been the arm. Yet dogs could not have been led to expect purgation from a subcutaneous injection, and Vulpian and Carville never failed to observe purgation in all the dogs with which they experimented. Moreover, the latter, as I have mentioned in an earlier part of this paper,[2] found, when he killed the animals before purgation had occurred, that the mucous membrane of the whole intestine was congested and inflamed, and covered with a sanguineous effusion. Evidently, therefore, Gubler's theory was insufficient.

It occurred to me that the true explanation of the action of a saline canthartic, when injected subcutaneously, lay in the salt producing irritation at the seat of its injection, which irritation through a form of reflex mechanism excited the peristaltic or secretory activity of the intestinal canal. The principle of treatment by counter-irritation must be founded on the recognition of an intimate nervous relation or sympathy between certain internal parts and other external, generally superjacent, parts. Between the parietes of the abdomen and its viscera such a nervous relation probably exists. It is this relation which is

[1] Bordier, Review in *Journ. de Pharmacie,* xx. 132 (1874).

[2] *Supra,* p. 8.

disturbed by the irritation of the injected salt. If the salt be injected in any other situation than beneath some portion of the skin in nervous relation with the abdominal contents, and that is probably any portion of the integument other than that which covers the abdomen, then purgation will not follow, for the nervous mechanism of the intestines is not disturbed. Hence, although Luton, Vulpian, and Carville invariably observed purgation occur when the salt was injected over the abdomen, yet Gubler's experiments were negative when the seat of the injection was the arm. This is more clearly proved by my own experiments, in which the situation of the injection was varied, and in which the following points will be demonstrated:—(1) A purgative salt is inactive when it is injected beneath the skin of the arm or leg; (2) when injected over the abdomen its cathartic effect depends upon its producing a certain degree of local irritation and inflammation, for when evidence of irritation is absent there is no purgation; (3) non-purgative salts, and one which, as chloride of sodium, exists naturally in large quantity in the blood, or one, as sulphate of zinc, which is astringent, also produce purgation, if their injection has been followed by local irritation.

Experiment LXXIX.—Terrier bitch, weighing 5·66 kilogrammes. Usual diet of bread, boiled flesh, and water continued throughout this and following experiments. Injected, in the forenoon, beneath the skin of the *back* between the scapulæ 0·2 gramme of crystalline *sulphate of soda*, dissolved in 2 c.c. of water.

During the following night a small quantity of hard fæces was evacuated. On the second night a similar evacuation again occurred.

There was not, at any time, perceptible swelling or inflammation of the subcutaneous tissue at the seat of the injection.

Experiment LXXX.—Same dog. Injected beneath the skin of the *abdomen*, two inches to the left side of the linea alba and one inch beneath the umbilicus, 0·1 gramme of *sulphate of soda* dissolved in 2 c.c. of water.

Neither during the following night or day did the animal defæcate. On the following night there was a stool of ordinary firm consistence.

There was no evidence of inflammation or pain at the seat of the injection.

Apparently in this dog sulphate of soda was incapable of purging, whether injected beneath the skin of the back or of the abdomen. It is, however, worthy of remark that in neither case was there any local irritation produced by the injection.

Experiment LXXXI.—Same dog: several days after previous experiment. Injected subcutaneously over the *abdomen*, inside the left flank, 0·1 gramme of *chloride of sodium*, dissolved in 2 c.c. of water.

The first evacuation occurred on the third day, and was of normal consistence.

There was no visible trace of inflammation at the seat of injection.

Experiment LXXXII.—Same dog. Injected subcutaneously over the outer side of the upper part of the left *fore-leg*, 2·4 c.c. of a solution of *sulphate of magnesia* containing 0·12 gramme of the salt.

There was a stool next morning, but small in quantity and perfectly firm. There was no further evacuation during the day.

There was no swelling at the seat of injection.

Experiment LXXXIII.—Same dog. Injected a similar quantity of the same solution of *sulphate of magnesia*, as used in the previous experiment, over the *abdomen*, inside the left flank.

Not until the second night was there any evacuation, and it was then small in quantity and quite hard in consistence.

There was no palpable or visible swelling or inflammation at the seat of injection, and apparently no pain.

Experiment LXXXIV.—Same dog. Injected, a few days afterwards, in the same situation, a like quantity of a solution of *sulphate of magnesia*, but double its strength, and containing, therefore, 0·24 gramme of the salt.

Although kept under observation for two days afterwards, no discharge of fæces took place during that time.

There was no detectable swelling of the injected part.

The sulphate of magnesia, therefore, like the sulphate of soda, failed to produce purgation, or even the slightest laxative effect, when injected subcutaneously in the same quantity and strength of solution as was used by Vulpian, not even when injected over the abdomen. Here, also, as with sulphate of soda, the injection was unaccompanied by local inflammation; and I have no doubt that this accounts for the negative results of my experiments as compared with those of Vulpian.

If these purgative salts failed to act, it was hardly to be expected that chloride of sodium could do otherwise, as the single experiment with it shows.

A few experiments were now made on cats.

Experiment LXXXV.—Cat, male, weighing 2·80 kilogrammes. Injected over the *back*, between the scapulæ, 0·15 gramme of *sulphate of soda*, dissolved in 1·5 c.c. of water.

No evacuation occurred during the two following days. When it did occur the discharge was hard.

No swelling or redness at point of injection.

Experiment LXXXVI.—Same cat. Injected beneath the skin of the *abdomen* 0·15 gramme of *sulphate of soda,* dissolved in 1·5 c.c. of water.

During the immediately succeeding night there was a fairly large and firm stool, followed by another firm evacuation on the next night.

No signs of irritation at the seat of injection.

The result of these two experiments with this cat and sulphate of soda is the same as of those with the dog—entirely negative.

Experiment LXXXVII.—Cat, female, weighing 1·64 kilogrammes. Passed a quantity of perfectly firm fæces immediately before the commencement of the experiment. At 1.10 P.M. injected subcutaneously over *abdomen,* near the umbilicus, 0·15 gramme of *chloride of sodium,* dissolved in 1·5 c.c. of water.

During the night a soft pultaceous stool was evacuated of the usual colour. On the following night there was another somewhat soft stool, but firmer than the other. By the next day the fæces had resumed their usual consistence.

A slight thickening of the subcutaneous tissue could be felt at the seat of injection, and was evidently painful on pressure.

Experiment LXXXVIII.—Same cat; a few days afterwards. Injected over the *back,* between the shoulders, 0·15 gramme of *sulphate of soda,* dissolved in 1·5 c.c. of water.

The first stool was evacuated on the second night after the injection, and was of perfectly firm consistence.

There was some swelling and pain in the neighbourhood of the injection.

These last two experiments were more successful than the others, inasmuch as in the one, by the abdominal subcutaneous injection of chloride of sodium, a purgative effect was obtained, and in both a certain degree of inflammatory irritation was produced at the seat of the injection. This local irritation, and not the absorbed chloride of sodium, was evidently the cause of the purgation in the one experiment. In the other, where the injection was made over the back, although sulphate of soda, a more purgative salt, was used, and notwithstanding that a similar degree of local irritation was induced, there was not the slightest laxative effect. These results certainly favour the theory I have advanced, as also do the following experiments with another cat.

Experiment LXXXIX.—Cat, male, weighing 3·05 kilogrammes. At 1.50 P.M. injected beneath the skin of the *abdomen*, to the inside of the left flank, 0·12 gramme of *chloride of sodium*, dissolved in 2·4 c.c. of water. The fæces passed previous to the experiment were observed to be firm.

There was a large evacuation during the night, partly firm and partly soft, although not liquid. One day later the fæces returned to their usual consistence.

There was slight swelling at the seat of the injection.

Experiment XC.—Same cat. Injected over the outer side of the thigh of the right *fore-leg* 0·125 gramme of *sulphate of magnesia*, dissolved in 2·5 c.c. of water.

There was no evacuation until the second night, when there was passed a small quantity of firm fæces.

Slight swelling at the seat of injection.

Experiment XCI.—Same cat; a few days afterwards. At 5 P.M. injected over the *abdomen*, to the inner side of the left flank, 0·12 gramme of *sulphate of magnesia*, dissolved in 2·4 c.c. of water.

During the night there was a large evacuation of fæces, half of which was firm and the other half much softer than usual, although not actually fluid.

There was not much visible inflammation at the seat of injection, although some thickening of the subcutaneous tissue could be felt. The pain on pressure seemed to be inconsiderable.

The chloride of sodium has again relaxed the bowels when injected over the abdomen; and a similar effect has followed the injection of the sulphate of magnesia in the same situation. On the other hand, the latter salt has not affected the stools when injected over a fore-leg. The degree of local irritation caused by the injection was not great, and was much alike in each of the three experiments.

Experiment XCII.—Cat, female, weighing 2·29 kilogrammes. Injected over the outer side of the thigh of the left *fore-leg* 0·1 gramme of *sulphate of magnesia*, dissolved in 2 c.c. of water.

No fæces during the next forty-eight hours—hard when they did appear.

Without there being much swelling at the point of injection, the animal seemed to suffer some pain when the part was pressed or rubbed.

Experiment XCIII.—Same cat; three days later. Injected over the *hypogastrium* 2 c.c. of a solution of *sulphate of magnesia*, containing 0·1 gramme of the salt.

The cat, which, without its being perceived, had been in an early stage of pregnancy, aborted in the course of the night. The consistence of

a small quantity of fæces, passed towards next evening, was softer than usual, but barely so much so as to be semi-fluid.

The injected part was somewhat swollen and painful.

The experiments on this cat, which in other respects present the same results as those on the previous cat, possess the additional interest of showing that the abdominal subcutaneous injection of a salt may cause the expulsion of the contents of the uterus, as well as those of the intestines, and probably by the local irritation of the injection acting on the uterus through the agency of a reflex mechanism similar to that which we have supposed to exist between the skin of the abdomen and the intestines.

Experiment XCIV.—Cat, female, weighing 2·09 kilogrammes. Injected subcutaneously over the outer side of the upper part of the right *fore-leg* 0·1 gramme of *sulphate of magnesia*, dissolved in 2 c.c. of water.

During the afternoon of the following day there was passed some solid fæces of ordinary consistence.

Experiment XCV.—Same cat; two days afterwards. At 7.10 P.M. injected over the *abdomen* 0·1 gramme of *sulphate of magnesia*, dissolved in 2 c.c. of water.

During the night there was an evacuation of a moderate quantity of soft semi-fluid fæces. On the following night more soft fæces were passed. By the third night the stools had resumed their usual consistence.

There was a little swelling and pain at the seat of the injection.

These two further experiments with sulphate of magnesia are, in their results, in harmony with those that precede, and leave little room for doubt as to the correctness of the theory I have advanced.

I have already shown that even chloride of sodium, a salt which forms the principal part of the ash of the blood, will cause purgation when injected over the abdomen, if its injection is at the same time followed by some degree of local swelling and inflammation. The quantity injected was so small in comparison with the amount of the salt normally present in the blood, that it is impossible to believe that the absorption of this minute quantity could exercise any effect upon the intestines Purgation must have been the reflex result of the local subcutaneous irritation.

That purgation, both in the case of the chloride of sodium and of the purgative salts, is produced by such irritation, some experiments with sulphate of zinc very fully support. Sulphate of zinc in small doses is well known to act as a powerful astringent, causing constipation in preference to purgation. Administered by the mouth to cats in doses of from 0·05 to 0·20 gramme, there was either no visible effect upon the stools, or, for a day or two afterwards, the stools were less frequent than usual, and their consistence was somewhat increased. When similar doses were injected subcutaneously over the legs, a like result was obtained. But, when the salt of the injection was the subcutaneous tissue of the abdomen, a laxative condition of the bowels always followed, although, in the two experiments instituted, more tardily than when sulphate of magnesia was employed. The details of these experiments follow.

Experiment XCVI.—Cat, female, weighing 2·49 kilogrammes. Injected subcutaneously over the *abdomen* to the inner side of the left flank, 0·5 c.c. of a 10 per cent. solution of *sulphate of zinc*, or 0·05 gramme of the salt.

The injection was made at noon, and by the same hour on the following day no fæces had been evacuated, although a slight swelling was visible at the seat of the injection. In the course of the evening of the same day there was a stool, which, although considerably softer than usual, was barely semi-fluid. The local swelling had not increased.

Experiment XCVII.—Same cat. Five days after the previous experiment a similar injection was made over the outer side of the left fore-leg, but without any laxative effect upon the bowels.

Experiment XCVIII.—Cat, female, weighing 2·09 kilogrammes. Injected over the *abdomen* to the inner side of the left flank, 1 c.c. of a 10 per cent. solution of *sulphate of zinc*, or 0·1 gramme of the salt.

Not until during the second night afterwards were any fæces evacuated, when there was a large semi-fluid, dark-coloured stool.

There was a considerable area of soft inflammatory swelling around the point of injection, which continued for a few days afterwards, without that the stools were again semi-liquid.

Experiment XCIX.—Same cat. After the swelling over the abdomen had completely subsided, a similar injection to that in the foregoing experiment was made over the *back* between the scapulæ.

There were no fæces for two days afterwards, and the first evacuation that occurred consisted of perfectly firm fæces.

These experiments, therefore, bear exactly out what I have

already predicated for them. The slowness in both instances with which the laxative effect followed the abdominal subcutaneous injection of the salt may be attributable to the salt by its absorption exercising its ordinary astringent impression upon the intestines, and thus delaying their evacuation until the salt has been eliminated from the circulation.

These now numerous experiments appear so clearly to establish the view I have suggested for the explanation of the action of minute doses of purgative salts subcutaneously injected, that it may be thought unnecessary that I should add to their number by giving a few experiments which were made on man. The only, yet perhaps sufficient, plea I can advance for proposing such an addition is, that it was on man that the first experiments on this subject were made by Luton, and that it was also on man that, later, Gubler performed the very large number of experiments which led to his rejection of Luton and Vulpian's explanation of their results. It became interesting, therefore, to know what effect the salt might possess when attention was paid to the locality into which it was injected. As the operation involved was of the simplest and most harmless nature, some of the experiments were made on convalescent patients within the wards of the Royal Infirmary; and for the performance of these I am indebted to Dr. Hosack Fraser, one of the assistants to the professors of clinical medicine. The remainder of the experiments were made on healthy individuals, and in every instance the person was of the male sex. In every experiment, unless where otherwise mentioned, 1 decigramme of sulphate of magnesia, dissolved in 1 c.c. of water, was injected. In order to test Gubler's theory, some of the patients were told that purgation was expected to follow the injections; the others were absolutely ignorant of the intention of the experiment.

In several cases the salt was injected beneath the skin of the arm; and in no single instance did purgation occur, although in the majority of the cases the individual was led to understand that such a result was expected. Very rarely was any trace of irritation perceptible at the seat of the injection. It is not necessary that I give further details of these experiments.

As to the results of the experiments when the salt was injected beneath the skin of the abdomen, sometimes purgation

followed, and at other times there was no effect. But, as a general rule, it was observed that, when the bowels were affected, the degree of local subcutaneous irritation was greater than when the stools were not softened. Most frequently in the latter case evidence of irritation was entirely absent. The following are the protocols of these experiments :—

Experiment C.—Sulphate of magnesia injected half an inch below the umbilicus. Patient not informed of the expected effect.

There was no purgation, and even no apparent acceleration of defæcation.

There was no trace of pain or swelling at the seat of injection.

Experiment CI.—Same in all respects as the preceding, and with exactly similar results.

No purgation, and no local pain or swelling.

Experiment CII.—Same as the previous two, but individual told that purgation was expected.

Results exactly as before; no laxative effect, and no local pain.

Experiment CIII.—Same conditions as in last experiment, and followed by precisely the same results.

Experiment CIV.—Same as previously, but individual not informed of the object of the injection.

On this occasion there was some degree of irritation and uneasiness at the seat of injection, and a slight laxative effect on the bowels made itself apparent next morning.

Experiment CV.—Same as in preceding experiment, but salt injected into the left iliac region.

A moderate amount of purgation occurred next morning, and there was some irritation at the locality of the injection.

Experiment CVI.—Similar in all respects to the last, and followed by much the same results.

Experiment CVII.—Injected below the umbilicus 0·05 gramme of *sulphate of zinc*, dissolved in half a cubic centimetre of water.

In the course of next morning there were two evacuations, both of them soft, but particularly the second, which was fluid.

There was an area of redness, more than an inch in diameter, round the point of injection.

Summary of the Experiments of Series F.

No. of Experiment.	Animal.	Salt Injected.	Situation of Injection.	Effect on Part Injected.	Effect on Bowels.
LXXIX.	Dog.	Sulphate of soda.	Back.	No inflammation.	No purgation.
LXXX.	do.	do.	Abdomen.	do.	do.
LXXXI.	do.	Chloride of sodium.	do.	do.	do.
LXXXII.	do.	Sulphate of magnesia.	Fore-leg.	do.	do.
LXXXIII.	do.	do.	Abdomen.	do.	do.
LXXXIV.	do.	do.	do.	do.	do.
LXXXV.	Cat, A.	Sulphate of soda.	Back.	do.	do.
LXXXVI.	do.	do.	Abdomen.	do.	do.
LXXXVII.	Cat, B.	Chloride of sodium.	do.	Slight inflammation.	Pulpy stool.
LXXXVIII.	do.	Sulphate of soda.	Back.	do.	No purgation.
LXXXIX.	Cat, C.	Chloride of sodium.	Abdomen.	do.	Stool, partly soft.
XC.	do.	Sulphate of magnesia.	Fore-leg.	do.	No purgation.
XCI.	do.	do.	Abdomen.	do.	Stool, partly soft.
XCII.	Cat, D.	do.	Fore-leg.	Slight pain.	No purgation.
XCIII.	do.	do.	Abdomen.	Slight inflammation.	Stool, partly soft. (Abortion.)
XCIV.	Cat, E.	do.	Fore-leg.	No inflammation.	No purgation.
XCV.	do.	do.	Abdomen.	Slight inflammation.	Semi-fluid stools.
XCVI.	Cat, F.	Sulphate of zinc.	do.	do.	Soft stool.
XCVII.	do.	do.	Fore-leg.	do.	No purgation.
XCVIII.	Cat, G.	do.	Abdomen.	Inflammation.	Semi-fluid stools.
XCIX.	do.	do.	Back.	Slight inflammation.	No purgation.
C.	Man.	Sulphate of magnesia.	Abdomen.	No inflammation.	do.
CI.	do.	do.	do.	do.	do.
CII.*	do.	do.	do.	do.	do.
CIII.*	do.	do.	do.	do.	do.
CIV.	do.	do.	do.	Slight uneasiness.	Slight laxative effect.
CV.	do.	do.	do.	Some irritation.	Moderate purgation.
CVI.	do.	do.	do.	do.	do.
CVII.	do.	Sulphate of zinc.	do.	Inflammation.	Purgation.

* Individual informed that purgation was expected.

A careful and unbiassed examination of these and the other experiments of this series amply prove, I venture to think, the propositions with which I started,[1] that the salt will not purge unless when injected over the abdomen; and that, even there, it will fail to act unless its injection is accompanied by a certain

[1] Page 130.

degree of irritation; and that its action depends, almost for certain, wholly upon such irritation, independent of the purgative quality of the salt.

In comparing the results of my experiments with those of Luton and Vulpian and Carville, it is somewhat remarkable that, even when I injected the salt over the abdomen, the bowels were by no means always affected, as seems to have happened in the experiments of these other observers; and, when they were affected, the purgation was of a very mild character, the stools being rarely more than partially liquid or semi-liquid. Indeed, had it not been that never once was an injection beneath the skin of the arm followed by the slightest laxative effect, I would have felt inclined to attribute the purgation occasionally observed after the abdominal injection to adventitious causes, and would have maintained that the subcutaneous injection *per se* of saline purges in any part of the body is absolutely without effect on the intestines. The only visible cause of purgation was the irritation which the salt produced at the seat of its injection. When this was entirely absent, no purgation was observed. At the same time, I am not prepared to assert that purgation or a laxative effect will always occur when irritation is visible; probably not. My own experience bears me out in this statement, as do also some experiments by Vulpian. There is, indeed, the possibility that, when the local irritation is intense, an opposite effect is produced upon the intestines, or, at any rate, that catharsis is not induced; for Vulpian on one occasion injected as much as 10 grammes of sulphate of magnesia, dissolved in 20 grammes of water, under the skin of the left flank of a dog; and in another dog, in the same situation, 4 drops of croton oil, dissolved in 10 drops of olive oil. In neither case was there any effect on the intestines, notwithstanding that in both animals there ensued extensive inflammation of the subcutaneous cellular tissue.

It may not be altogether unprofitable to inquire by what means, or through what mechanism, the subcutaneous irritation contrives to cause purgation. The mechanism, as I have already suggested, cannot well be other than nervous and reflex. The abdominal wall has no direct organic connection with the viscera which it covers. The subcutaneous irritation must produce such an impression on the sensory nerves of the abdominal wall as

will be conveyed to some centres in the spinal cord or encephalon in immediate relation with other nerve centres, whose efferent fibres pass to the intestines, and through which the impression will be reflected to these viscera. So much is tolerably certain. But whether the efferent nerves are such as control the secretion of the intestines, or are those which regulate peristalsis, or, perhaps, are merely the vasomotor nerves of the gut, my experiments do not afford me much help in deciding. The stools were not sufficiently fluid as to lead me to believe that secretion was much, if at all, affected. Their character more inclined me to think that it was the motor nerves that were influenced—not only of the intestines, but also of the uterus (Experiment XCIII.). But Carville's observation of a highly congested condition of the intestines in dogs killed shortly after the abdominal subcutaneous injection of sulphate of magnesia, to which I have already referred,[1] renders it probable that it is the vasomotor nerves which are inhibited, giving rise to a temporary catarrhal condition of the intestines. This probability is strengthened by common experience in other departments of medicine, in which we are not unacquainted with an intimate sympathy existing between parts, superficial and deep, totally unconnected by nerves or vessels passing directly between them, and where irritation of the former or superficial or cutaneous part may lead to a vasomotor disturbance of the latter, resulting in congestion and even in inflammation. I need but adduce the instance of the lungs and the skin of the thorax. Hardly any one doubts that congestion and inflammation of the former may sometimes arise from stimulation of the latter by cold or damp; and it has been occasionally observed that a burn or scald of the skin of the thorax has been followed by congestion and inflammation of the underlying portion of the lung.[2]

In citing the instance of the sympathetic relation of the thorax and the lungs, and its affection by cold, as comparable to what occurs when the irritation of an abdominal subcutaneous injection disturbs the vasomotor nerves of the subjacent viscera I am aware that many physicians would maintain that, in the former case, the application of cold to the skin of the thorax does not produce congestion of the lungs through a reflex nervous mechanism consisting of the cutaneous nerves of the thorax and

[1] Page 129. [2] Spence, *Lectures on Surgery*, 2nd edit., p. 176; and others.

the vasomotor nerves of the lungs. They believe that the cold causes contraction of the cutaneous arterioles, and, driving more blood into the visceral circulation, produces a purely dynamical and compensatory expansion of the arteries of the subjacent lung, no other mechanism being involved than the blood-vessels and the circulation. This, however, is in the highest degree improbable. For, if the volume of the cutaneous circulation be diminished, and that of the visceral circulation correspondingly augmented, why should the lungs alone be congested, and the remainder of the internal organs remain uncongested? And, indeed, it is very problematical, if congestion of any internal organ, as we ordinarily understand it, can be caused by a rapid, and much less a gradual, increase of the volume of its blood-supply within such limits as are likely or possible to occur; for physiology teaches us that, owing to the great dilatability of the veins, both trunks and branches, the capacity of the circulatory system is capable of undergoing sudden and most extensive variations without visible congestion or inflammation of any organ being produced. Were it otherwise, congestion and inflammation of organs would be of frequent occurrence after the application of an Esmarch bandage to the whole length of a lower limb in so-called "bloodless" surgery; and simple transfusion of blood might be attended with the gravest results. Irritation, therefore, of the skin, be it produced by cold, burns, or subcutaneous injections, causes congestion of certain internal, generally subjacent, viscera, not from any disturbance in the equilibrium of their blood-supply acting through the circulation, but from stimulation of a nervous mechanism, which, through the central nervous system, brings the viscera into close union and sympathy with certain cutaneous areas, and through which mechanism vasomotor paresis of the viscera may occur. Thus the abdominal subcutaneous injection of a solution of sulphate of soda, sulphate of magnesia, chloride of sodium, or sulphate of zinc, in proportion to the nature and degree of the local irritation it produces, can cause congestion of the intestines and consequent diarrhœa; whilst, if it be injected in some region of the body, between which and the abdominal viscera there exists no intimate nervous connection, the injection, however it may affect other organs, will exert no reflex action on the vasomotor supply of the intestines.

Vulpian's experiments render it probable, as I have already remarked, that a very strong irritation of the abdominal cutis does not produce upon the intestines the effect of a weaker irritation. The former may, by exciting a larger area of nervous centres in the brain or spinal cord, bring into play efferent fibres, other than the vasomotor inhibitory, which may nullify the action of these; or, without assuming the involvement of more nerve centres and fibres, it is possible, from the consideration of other physiological and pharmacological phenomena, that an intense stimulation of the same nervous mechanism may have the opposite effect of a weak stimulation.

The explanation which I have offered of the purgative action of a salt when injected subcutaneously is of considerable interest in connection with an observation by Köhler in his elaborate paper on the action of elaterium.[1] Zwicke, one of his pupils, he remarks, had found that injection of an alcoholic solution of convolvulin under the skin of the back, or directly into the vena jugularis, was not capable of purging; injected, however, under the skin of the abdomen, purgation constantly followed. This difference in the behaviour of the cathartic, Köhler attributes to the solution of the convolvulin, in the latter case, directly penetrating the thin abdominal parietes by a kind of endosmotic action, and thus reaching and entering the intestine without the intervention of the blood-vessels. In the intestines it came in contact with the bile, and was enabled to exert its usual purgative effect, convolvulin being one of those resinous cathartics to which Buchheim and his pupils first directed attention as producing their characteristic action only when mixed with bile. With all respect for the extensive pharmacological experience of the late and lamented Köhler, the explanation he offers of convolvulin, when thus injected, is to my mind very unsatisfactory and extremely improbable. Can he ask us to believe that the alcoholic solution of the resin will find some path by which it can wander through the muscular wall of the abdomen, through the powerfully absorbent cavity of the peritoneum, and, finally, through the intestinal wall, without in its course being completely absorbed by the numerous blood-vessels and lymphatics it is forced to pass? A much more likely explanation is that which

[1] Köhler, *Archiv f. patholog. Anat.*, Bd. i. s. 379; Zwicke, *Wirk. d. Convolvulins u. Jalapins*, Inaug. Dissert., Halle, und *Berl. Klin. Woch.*, 1870, No. 17.

I have suggested for the action of a similarly injected salt; the alcohol and the convolvulin locally irritate the cutaneous nerves of the abdomen, and reflexly inhibit the vasomotor nerves of the intestinal canal. Köhler observed that much the same effects followed variously seated injections of an alcoholic solution of elaterin, as when convolvulin was employed.

If I might present yet another instance of purgation following irritation of the abdominal parietes, it is the ancient and long-practised custom of purging children and others by rubbing the abdomen with an irritant cathartic.[1] Since the introduction of croton oil, it has been largely used for this purpose, and notwithstanding the incredulity of Buchheim [2] and some others as to its action being manifested when thus applied, there is no reason to doubt its being able to purge, as otherwise it is difficult to understand how the practice became at one time so prevalent. It was the apparent impossibility of the absorption of the oil by the skin which led such observers as Buchheim to doubt the capability of its acting by *absorption*, and in this they were probably right. For the most recent investigators of the absorptive power of the skin deny its ability to absorb even the most diffusible substances, provided they are non-volatile.[3] But, according to my view, absorption is not requisite, the irritation caused by the application of the oil to the skin being sufficient to account for purgation. And, while its inunction over the abdomen is succeeded by catharsis, I am not aware that its application to the chest in thoracic disease has been observed to be followed by a similar effect, although an equal opportunity is presented for its absorption; and according to some old but apparently reliable experiments by Lund,[4] the oil purges when rubbed over the umbilicus, but not when applied to the arm.

Not only do the experiments of this series furnish a reasonable explanation of the results of other observers working with entirely different purgatives, but I claim that the latter even support the view I have derived from a consideration of the former.

[1] Mérat et Lens, *Dict. univers. de matière médicale*, art. Purgatifs, t. v. p. 544; Madden (*On Cutaneous Absorption*, Grad. Thesis, Edinburgh, 1838, p. 91) cites various authors as stating that a solution of jalap, rhubarb, or scammony, applied to the abdomen, was frequently followed by purgation.

[2] Buchheim, *Arzneimittellehre*, 3 Aufl., 1878, s. 378.

[3] *Vide* Röhrig, *Physiologie der Haut*, Berlin, 1876.

[4] Lund, *De oleo crotonis*, Dissert. Inaug. Halis Sax., 1831, pp. 21 *et* 38.

The most important objection to the saline cathartics acting by absorption when subcutaneously injected lies not in the results of the experiments of this series, but in those of the preceding series, where it was fully demonstrated that a saline cathartic is not capable of purging when injected into the blood.

Series of Experiments, G.

The effect of the salt on the blood and the circulation; as also its effect on the temperature of the body.

I have already in Series C. drawn attention to the fact that the blood becomes concentrated for a short time after the administration of a strong solution of sulphate of soda. A second concentration, but of less degree, is observed several hours later. At neither stage, however concentrated the blood may be, have I ever perceived any crenation of the corpuscles, if they were examined immediately after the blood was taken from the body; but, if the blood was allowed to remain for a few minutes beneath the cover-glass on the microscopical slide, I have often observed that the corpuscles of the concentrated blood became more or less crenated, whilst within the same time the corpuscles of ordinary blood did not exhibit the slightest appearance of crenation. This is a point almost devoid of interest, since the crenation does not occur within the body.

The supposed alteration of the proportion of the white to the red corpuscles produced by the administration of a saline purgative is of more importance, although the mode of its production and its effect on the body are quite unknown. I have myself made no observations relative to this alteration, as the distribution of the leucocytes in a drop of blood is so unequal that the average of a very large number of enumerations of the corpuscles is necessary to obtain even an approximate knowledge of their proportion in the blood. Ch. Robin, from direct observation, is of opinion that "a simple diarrhœa, such as that caused by the administration of a purgative, as Seidlitz water, suffices to produce a notable augmentation of the leucocytes."[1] On the other hand, Brouardel,[2] as the result of a number of experiments on

[1] Ch. Robin, *Op. cit.—supra*, p. 90.
[2] Brouardel, *Op. cit.—supra*, p. 90.

man, finds that after the administration of saline and other purgatives the absolute number of the leucocytes in the blood is sometimes diminished, at other times increased, but that in relation to the red corpuscles their number is almost without exception diminished. In each experiment the enumeration of the corpuscles in the blood was made in ten different portions of the microscopic field by every member of Brouardel's histological class, each with a separate portion of blood, so that Brouardel's observations are as trustworthy as can be obtained by the method at our disposal. It is to be remarked that both Brouardel and Robin examined the blood several hours after the administration of the purgative, and in most cases during that period in which I observed the secondary concentration of the blood. It is, however, highly probable that the alteration of the numerical relation of the white to the red corpuscles is in no way connected with the condition of concentration, but proceeds from the presence of the purgative in the blood affecting the transformation of the white into the red corpuscle, or disturbing the production of the white corpuscle in those localities of the body where it is believed to originate; and it is equally probable that the change is gradually accomplished, and, therefore, will have produced no perceptible effect, during the stage of primary concentration.

The blood, so far as I have observed, suffers no other physical or chemical change, except the alteration in its composition due to the presence of the salt. It will be remembered that I suggested, as the result of the experiments of Series D., that during the first hour after the administration of the salt the blood is probably highly charged with the salt, and that later the salt in great part disappears, mainly on account of its reappearing within the intestines. I may here state that since these experiments were made I have chemically estimated the amount of the salt recoverable from the blood at various periods after its administration, but have not been able, so far, to obtain evidence of a marked variation in the quantity of the salt in the blood. The result of these and other experiments will form the subject of a future communication.

The change in the metabolism of the body, which is intimately associated with the action of the salt on the blood, will be considered along with the effect of the salt on the urinary secretion.

There is still another action, or supposed action, of the purgative, which may be appropriately considered in connection with the blood. Does the administration of a saline cathartic affect the temperature of the body? Purgatives, and particularly saline purgatives, have long been used in the treatment of fever, under the impression that, among other effects, they help to cool the body. For the purpose of ascertaining if a saline cathartic actually reduces the temperature of the body, I made two experiments on man, a third on a cat, and a fourth on a rabbit. Although not sufficient in number to furnish a perfectly definite conclusion, yet they present fairly substantial grounds for inferring that the salt has little effect on the temperature. In two of the experiments, there was administered on the previous day, with the object of learning the mere effect of the cold water of the salt solution, a quantity of cold water equal in bulk and temperature to the salt solution given. The two individuals submitted to the experiment partook of breakfast at 8.30 A.M., and received no food until 4.30 P.M. In the case of the cat and the rabbit, they had no food on the day of the experiment until after eight in the evening. And on those days on which the

Experiment CVIII. *Experiment CIX.*

A.B., æt. 26. Temperature of Room, 10°–11° C.						C.D., æt. 46. Temperature of Room, 16° C.			
First Day.		Second Day.		Third Day.		First Day.		Second Day.	
Normal.		Effect of Water.		Effect of Salt Solution.		Normal.		Effect of Salt Solution.	
Time.	Temp.	Time.	Temp.	Time.	Temperature.	Time.	Temp.	Time.	Temperature.
A.M.	°C.	A.M.	°C.	A.M.	°C.	A.M.	°C.	A.M.	°C.
10.30	36·2	10.40	35·9	10.20	36·0	11.45	36·9	11·25	36·7
P.M.		P.M.		P.M.		P.M.		P.M.	
12.5	36·3	12.20	36·1	12.5	36·2	...	...	12.10	36·7
2.0	36·3	2.10	36·3	2.0	36·1	...	...	12.15	Salt solution.
...	...	2.28	36.3	...	...	...	...	12.30	36·6
2.30	36·2	2.30	Water.	2.30	Salt solution.	...	...	12.45	36·65
...	...	2.35	34·6	...	...	1.0	36·8	1.0	36·65
3.0	36·3	2.40	35·7	2.40	35·5	...	...	1.30	36·7
...	...	3.30	36·2	3.40	35·8	2.0	36·7	2.30	36·7
4.30	36·1	4.30	36·2	4.25	36·1	3.0	36·6	3.30	36·7
9.0	36·3	9.0	36·4	9.0	36·2	4.0	36·6	4.30	36·6
...	..	...	...	...	...	8.30	36·9	8.30	36·5

course of the normal temperature was obtained, and the course of it as affected by a drink of cold water, the same restrictions as to diet were imposed. The temperature was taken beneath the tongue of the men, and in the rectum of the rabbit and cat, and two observations were in most cases made at each period, the one to correct and confirm the other.

In Experiment CVIII., 600 c.c. (20 oz.) of water at 5° C. were given on the second day at the time indicated; and 15 grammes (fully $\frac{1}{2}$ oz.) of sulphate of soda, dissolved in 600 c.c. of water, the solution having a temperature of 5° C., were administered on the third day. In the other experiment, 28 grammes (1 oz.) of sulphate of magnesia, dissolved in 250 c.c. (fully 8 oz.) of water, the temperature of the solution being 2° C., were given on the second day.

Experiment CX. *Experiment CXI.*

Rabbit, male; 1·7 kilogrms. Temperature of room, 10° C.						Cat, male; 3·1 kilogrms. Temperature of room, 10° C.			
First Day.		Second Day.		Third Day.		First Day.		Second Day.	
Normal.		Effect of Water.		Effect of Salt Solution.		Normal.		Effect of Salt Solution.	
Time.	Temp.	Time.	Temp.	Time.	Temperature.	Time.	Temp.	Time.	Temperature.
A.M.	°C	A.M	°C.	A.M	°C.	A.M.	°C.	A.M.	°C.
11.0	38·3	11.10	38·4	11.10	38·1	11.15	38·8	11.20	38·5
P.M.		P.M.		P.M.		P.M.		P.M.	
...	...	1.40	38·4	1.25	38·2	12.50	38·6	1.35	38·4
...	...	1.50	Water.	1.45	Salt solution.	2.20	38·7	2.20	Salt solution.
2.0	38·2	2.10	38·2	2.15	37·7	...	...	2.45	38·1
...	...	...	...	2.25	37·8	...	...	3.15	38·2
...	...	2.45	38·4	2.50	37·9	3.40	38·5	3.45	38·6
...	...	3.30	38·5	3.50	38·2	...	...	4.15	39·0
4.0	38·1	...	...	4.10	38·6	5.30	38·6	5.15	39·3
...	...	..	...	5.10	38·3	...	...	6.25	39·4
6.0	38·3	...	...	6.20	38·5	...	...	7.35	39·2
8.0	38·1	7.0	38·8	7.25	38·5	...	...	...	...

In both experiments the salt administered was the sulphate of soda, and in equal strength of solution, namely, 10 per cent., and of like temperature—7·5° C., 50 c.c. having been given to the rabbit, and 40 c.c. to the cat. 50 c.c. of water, of the same temperature as the salt solution, were administered at 1.50 P.M. on the second day of Experiment CX.

In all these experiments a purgative discharge did not occur

during the period in which the temperature was recorded, but in all of them, except that with the rabbit, free purgation followed in the course of the evening.

Before drawing any conclusion from these experiments, I have to remark that, from several unrecorded observations of the daily course of the normal temperature of the animals employed, I found that the temperature of the same animal often varied very considerably from day to day, as also throughout any single day. Too much importance is not, therefore, to be attached to the variations observed during each experiment. We may, however, reasonably conclude from these experiments that the solution of the saline cathartic generally produces, almost immediately after its administration, a slight reduction of temperature, which never amounts to more than half a degree Centigrade, or about one degree Fahrenheit, and which continues, gradually becoming less evident, from one to two hours. The temperature having reached the normal, remains at this, or, if anything, mounts higher (Exps. CX. and CXI.). It is probable, however, that the later rise of temperature observed in these experiments was due to causes other than the administration of the salt. In certain circumstances, as in Exper. CIX., the temperature is scarcely affected; this is probably exceptional. Water, it will be observed, given in a quantity, and of a temperature, equal to those of the salt solution, also distinctly lowers the temperature of the body, but barely to the same extent as the salt solution, and evidently not for so great a length of time.

A saline cathartic would, therefore, appear to exert no, or very little, lowering effect on the temperature beyond that produced by an equal quantity of cold water. The slightly greater effect of the saline solution and its more protracted action are probably to be attributed to the absorption of heat which occurs when the solution is diluted by its mixture with the fluid contents or secretion of the alimentary canal and with the blood, a solution of a salt absorbing heat, or being reduced in temperature, when it is diluted.

But, although the degree of the general temperature of the body, or the temperature of the internal organs, is not affected by the salt, it seems almost to be otherwise with the absolute

heat or caloric of the body. For it is common experience that for several hours after the administration of a saline cathartic, and for many hours beyond the actual observed depression of temperature, there is a decided feeling of chilliness, sometimes accompanied by slight shiverings, the extremities often becoming extremely cold. This is not a mere subjective sensation of cold; for it is not difficult to ascertain that the temperature, for example, of the hands, is much lower than usual. Yet the temperature of internal and unexposed parts remains high. This loss in the absolute heat of the body is probably caused by a contraction of the peripheral arteries due to the slightly irritating action of the salt dissolved in and circulating with the blood. A full supply, therefore, of warm blood is denied to the peripheral parts of the body, and these being exposed to the cold of the surrounding atmosphere quickly lose their heat.

In so far, therefore, as its effect on the temperature is concerned, the advantage of the employment of a saline cathartic in the treatment of fevers is extremely doubtful; for, although the peripheral temperature is reduced, the temperature of the blood and of the viscera, on which the effect of a high temperature is most dreaded, is not lowered.

The supposition made in explanation of the salt reducing the temperature of the periphery of the body, namely, that the arterioles have their calibre diminished, receives support from observations I have made of the action of the salt on the circulation, to the consideration of which I now proceed.

In estimating the effect of the saline cathartic on the circulation I have confined myself to observing the effect on the pulse by means of Marey's sphygmograph. No direct experiments were made as to the action of the salt on the actual arterial blood-pressure, owing to the fact that, from sphygmographic observations, I knew the effect on the circulation was very gradually produced, and was probably at no time very marked; and in such a case I believed that the effect of the prolonged subjection of the animal to the requirements of a blood-pressure experiment, and the disturbance produced by the necessary administration of anæsthetics, would almost certainly obscure the action of the salt.

The prevalent belief has long been that cathartics, salines in-

cluded, lower the blood-pressure. And it is more with this object than from any anticipated effect on the temperature that cathartics have been employed in the treatment of acute febrile and inflammatory conditions, it being supposed that, by removing through the intestines from the blood a quantity of its fluid, they accomplish a form of depletion which results in a diminution of the volume of the blood and consequently of its pressure. This supposition is based on the erroneous assumption that a very gradual and not too extensive depletion of the blood is followed by a lowering of the blood-pressure. Still it is possible that, quite apart from this supposition as to the method of its production, cathartics may lower the blood-tension. Lauder Brunton[1] gives two sphygmographic tracings of the pulse of a healthy man, one taken before, and the other after, the action of a purgative, which lend support to the common belief. The name of the purgative used is not stated. My own observations are more numerous than those of Brunton, and in their results they seem to contradict those of that eminent pharmacologist. I, of course, employed saline purgatives, and observed their effect on the tension and rate of the pulse, and, as in Lauder Brunton's experiment, in individuals with a normal circulation. The observations were made on the patient submitted to Experiments LIV. and LV., in both of which sulphate of soda was the salt employed, and on a second patient in the wards of the infirmary to whom a dose of sulphate of magnesia was administered. The sphygmographic tracings from the former patient were taken whilst the previous experiments were in operation.

Experiment CXII.—J. W., æt. 33, suffering from a chronic nervous disease of an ataxic character; general health otherwise good. The patient was placed in bed about twenty minutes before the first tracing was taken, and was kept in bed throughout the experiment. The sphygmograph (Marey's) was fixed with a comparatively light pressure over the left radial artery at the wrist, the arm being kept all the while steadily in the same place on the bed, and the sphygmograph was not moved from its original position until all the tracings had been taken, except that, immediately after taking the last tracing of the series presented, it was moved gently about for the purpose of ascertaining if the character of the tracing was not due to a change having occurred in the position of the instrument. But, although

[1] Lauder Brunton, *Practitioner*, vol. xii., 1874, p. 417.

several other tracings were taken, they did not differ in character from the one first procured. No food was given during $4\frac{1}{2}$ hours previous to the administration of the purge—21·3 grammes ($\frac{3}{4}$ oz.) of sulphate of soda dissolved in 85 c.c. (3 oz.) of water, or nearly a 20 per cent. solution of the salt. Purgation occurred next morning, fully 14 hours afterwards. A large series of tracings were taken, a few of which are reproduced. The following letters refer to those of the accompanying lithograph (Plate X.).

A. 10 minutes *before* the administration of the purgative.	Pulse, 60 ;	resp. 20.
B. 60 minutes *after* ,, ,, ,, ,,	Pulse, 56 ;	resp. 20.
C. 125 minutes ,, ,, ,, ,,	Pulse, 60 ;	resp. 26.
D. 185 minutes ,, ,, ,, ,,	Pulse, 56 ;	resp. 24.

A tracing was taken $9\frac{3}{4}$ hours after the administration of the purgative, the pulse being 52, and respiration 24 ; it was almost exactly the same in character as D.

Experiment CXIII.—Same individual as in previous experiment and conditions exactly alike, excepting that the salt was given dissolved in 454 c.c. (16 oz.) of water—about a 5 per cent. solution. A free watery purgation occurred two hours afterwards.

The series of tracings obtained during this experiment was similar in character to that of the previous experiment, except that the gradual change observed to occur in the form of the pulse-wave, although quite evident, was not so well marked. The rate of the pulse and the respirations was very little affected, falling very slightly after the administration of the salt, the former from 60 to 58, and the latter from 12 to 20.

Experiment CXIV.—W. F., æt. 19, convalescent from nephritis. Conditions were quite the same as in the previous experiments. The purgative administered was 21·3 grammes ($\frac{3}{4}$ oz.) of sulphate of magnesia, dissolved in 227 c.c. (8 oz.) of water—about a 10 per cent. solution. Purgation took place $2\frac{1}{2}$ hours afterwards, and was followed by another watery dejection a few hours later in the evening. The following numerals refer to those of the accompanying lithograph, in which a few of the spygmographic tracings taken are represented.

I. 7 minutes *before* the administration of the purgative.	Pulse, 92 ;	resp. 20.
II. 60 minutes *after* ,, ,, ,, ,,	Pulse, 82 ;	resp. 18.
III. 143 minutes ,, ,, ,, ,,	Pulse, 84 ;	resp. 20.
IV. 225 minutes ,, ,, ,, ,,	Pulse, 79 ;	resp. 17.

The pulse-wave, as obtained by the sphygmograph, is not always a very reliable index of the blood-pressure ; yet, as the present observations were made with the greatest care, and with the assistance of Dr. Logan, a former resident physician in the infirmary, and who had considerable experience in the use of the sphygmograph whilst assisting Professor T. R. Fraser, we are entitled to regard these tracings as fairly representing the state of the pulse. In each case, the pressure of the sphygmograph

remaining constant, the instrument was so placed as to obtain the greatest possible movement of the lever, and in this position it was maintained during the experiment. When it was removed to permit of the patient going to stool, as happened in the last two experiments, it was afterwards placed in exactly the same position, and gently moved about until it rested on the point which gave the maximum movement of the lever. In each experiment many more tracings were taken than those reproduced, and all of them showed progressively the changes seen in those selected.

In the first place, it will be observed that the frequency of the pulse cannot be said to be much altered ; if there be any change it is towards a slowing of the pulse. It is otherwise with the tension of the pulse, particularly in the first of the three experiments where each successive tracing indicates a progressive increase of the arterial tension, most evident in the third and following tracings. The same effect was observed in the second experiment, although not so markedly. The great difference in the degree of the concentration of the solution of the salt administered in these two experiments producing a remarkable difference in the degree of the concentration of the blood (*vide* Experiments LIV. and LV.) may account for the difference in the pulse. The lessened total volume of the blood in the first experiment is, almost contrary to expectation, associated with a more decided increase of the tension of the pulse. But whether this greater rise is to be attributed to the concentration of the blood, or to the absorption and presence of more salt in the blood than in the second experiment, it is difficult to say.

In the third experiment, that in which sulphate of magnesia was administered, an increase of the tension of the pulse is also apparent. I regret that, owing to the discharge of the other patient from the hospital, I was unable to make this experiment also on him, so that a better comparison might have been instituted between the action of the soda salt and that of the magnesia salt. The frequency of the pulse is in this experiment decidedly lessened, but this may have been accidental.

The rate of the pulse, judging from these and other experiments, becomes usually a little slower after the administration of the salt, but often it is not at all affected.

If I am correct in interpreting the changes observed in the pulse-tracings as indicating an increase of the arterial pressure, it falls to be asked how this increase is accomplished. It is probably due, as I have already hinted, to the irritation of the walls of the arteries, particularly of the smaller arteries, by the salt, which the blood has absorbed, producing a contraction of their calibre, and thus increasing the resistance to the onward flow of the blood. The nature of the alteration of the pulse-wave points more to a diminished outflow of blood through the arterioles than to an increased inflow from stimulation of cardiac action. If the heart participate in effecting the increase of the blood-pressure, the rate of its pulsations shows that it is not by any increase of their frequency.

What then is the value of the cathartic in inflammation, if it increases the blood-pressure within the inflamed organ? Increase of arterial pressure, however, does not necessarily imply increase of pressure within the capillaries, if the increased pressure be due to the contraction of the arterioles. It may, on the contrary, be associated with a diminished capillary pressure; and this is probably what occurs after the administration of a saline cathartic. But, even should the salt increase the pressure of the entire blood system of the organ, it is possible that as much benefit may be derived from a more forcible and penetrating circulation, driving onwards the stagnating blood, as from a diminution of pressure. How else can digitalis prove so beneficial in cases of inflammation and fever, if we accept the results of some recent continental experiments on the nature of the action of this remedy?

Series of Experiments, H.

The effect of the salt on the urinary secretion.

The experiments of this series are, like those of the last series somewhat fragmentary, and do not pretend to do more than roughly indicate the probable mode of action of the saline purgative on the urine.

This action requires to be considered with reference to the effect of the salt on the rate of the secretion of the urine, and its effect on the chemical composition of the urine. The immediate effect of the administration of a dose of a saline purgative on the

secretion depends considerably on the degree of dilution of the salt given. If the solution is very concentrated, the amount of urine secreted during the next few hours is often somewhat diminished, owing to a partial metastasis of the secretion. But quite as frequently the rate of the secretion may not at all be affected. If, however, the solution is very dilute, there is an immediate increase of the secretion, which continues for a short time, until the excess of water taken with the purgative has been eliminated by the kidneys. But whether the salt solution administered be dilute or concentrated, unless extremely dilute, there is frequently observed, during the twelve hours or so immediately following the injection of the purgative, a diminution of the total amount of the secretion. This diminution is probably dependent on the fluids of the blood having been largely removed during this time by purgation. This effect, however, is not constant, and is not exhibited in all of the experiments selected to illustrate this series. Sooner or later the diminution of the secretion, if it occur, is succeeded by a generally well-marked increase, which usually begins to be evident within twelve or fifteen hours, or more, after the administration of the purge, and which continues for a complete day, or longer, afterwards. This is well illustrated in Experiment XXIII. of Series A., and in Experiments LIV. and LV. of Series C., and in some experiments whose details I shall immediately give, in all of which care was taken that the daily amount of fluids imbibed was as nearly as possible constant. This diuretic effect of the salt is accompanied by a tolerably distinct concentration of the blood, as I have previously pointed out (Series of Experiments, C.).

The effect of the saline cathartic on the quality or composition of the urine is, apart from the alteration produced by its own presence, not great, and will be best appreciated after considering the results of the subjoined experiments.

In the first of the experiments of this series the action of a very dilute solution of sulphate of soda on the rate of the urinary secretion will be exhibited and contrasted with the normal rate of secretion, and with the effect of water, equal in quantity to the salt solution administered. This, as well as the two subsequent experiments, I conducted on myself; and whilst they were being made I took care that, for some days previously,

my diet, and particularly the liquids of it, should be of the same quality and quantity on each day; as far as possible, also, the amount of physical exercise, and the nature of my occupation, were similarly regulated. Breakfast was taken about 8.30 A.M., and dinner not until 5.30 or 7.30 P.M., no food having been eaten in the interval, and no supper afterwards. No fluids were consumed unless at meals, and then sparingly. In this way it was possible to procure a tolerably steady rate of urinary secretion. The urine was usually collected, by a complete evacuation of the bladder, every half hour during the afternoon, the salt not being administered until about four hours after breakfast, so that the stomach might be fairly free from food, the breakfast being light and easily digestible.

Experiment CXV.—In the accompanying tabulated arrangement of the results of this experiment, at each hour bracketed in the first day of the B. part of it, 100 c.c. of a solution of sulphate of soda were drunk, containing 3 grammes of the salt, and at the same hour in the C. part, 100 c.c. of ordinary spring water were taken. The bladder was evacuated every half hour from 12.30 to 7.30 P.M. From 7.30 P.M. until 8.30 next morning it was evacuated at irregular intervals, but the whole of the urine was measured, and from it was estimated the half-hourly average. From 10.30 A.M. to 12.30 P.M. the bladder was emptied hourly. The sulphuric acid of each of the half-hourly evacuations was estimated by boiling the urine with hydrochloric acid, and afterwards precipitating with barium chloride in the usual manner, and with the usual precautions. On account of the urine having been previously boiled with hydrochloric acid, both the "gepaart" and "ungepaart" sulphuric acid was precipitated. The excess represented in the table, and calculated as sulphate of soda, is the excess of the acid due to the presence of the purgative salt. The normal proportion of the acid was estimated during the hour previous to commencing the experiment. The quantity normally excreted very gradually becomes less during the afternoon, but the fall is not sufficient to impair the general accuracy of the results given.

A moderately soft stool was passed about 8 P.M. of the same day on which the salt was taken.

It will be observed from the results of this experiment that the drinking of 400 c.c. of a 3 per cent. solution of sulphate of soda produces an immediate increase in the flow of urine, although not by any means in proportion to the amount of fluid taken, and very much less in amount than that caused by the drinking of the same quantity of water, when, indeed, allowing for the normal amount of secretion, more urine was secreted than there

has taken of water. The immediate increase of the urine, which sollows the administration of the salt, gradually but quickly disappears, and is followed by a remote increase, which commences in the course of the night and is apparent during the greater part of the following day.

The rate of the elimination of the salt in the urine is of

Experiment CXV.

Time of Evacuation of Bladder.	Half-hourly Rate of Secretion of Urine.				Sulphates estimated as $Na_5SO_4.10H_2O$ recovered from Urine of B.	
	A. Normal.	After Administration of				
		B. Sulphate of Soda.		C. Water.		
		First day.	Second day.		Total.	Excess.
...	c.c.	c.c.	c.c.	c.c.	grms.	grms.
10.30 A.M.	...	...	...	...	...	...
11.30 ,,	24	19	29	20	...	...
12.30 P.M.	22	20	32	23	0·1200	...
[12.32 ,,]	...	[100 c.c. of salt solution]	...	[100 c.c. of water]	...	...
1 ,,	20	32	28	36	0·1989	0·0789
[1.2 ,,]	...	[100 c.c. of salt solution]	...	[100 c.c. of water]	...	..
1.30 ,,	19	32	30	72	0·1972	0·0772
[1.32 ,,]	...	[100 c.c. of salt solution]	...	[100 c.c. of water]	...	...
2 ,,	16	48	28·5	172	0·1964	0·0764
[2.2 ,,]	...	[100 c.c. of salt solution]	...	[100 c.c. of water]	...	...
2.30 ,,	16	51	26	168	0·1968	0·0768
3 ,,	15	35	25	109	0·2168	0·0968
3.30 ,,	15	31	25	94	0·2232	0·1032
4 ,,	14·5	28	26	56	0·2290	0·1090
4.30 ,,	13	22	24	31	0·2172	0·0972
5 ,,	13·5	24	23	22	0·2600	0·1400
5.30 ,,	12	23	17	18	0·2582	0·1382
6 ,,	11	16	16	13	0·2213	0·1013
6.30 ,,	11	11	15	12	0·2189	0·0989
7 ,,	11·5	10	14	11	0·2046	0·0846
7.30 ,,	11	10	12	10	0·2032	0·0832
10.30 A.M.	28	30	31	25	Total Excess	1·3617

particular interest in connection with the experiments of Series D., where the conclusion was arrived at, that, at least, the acid of the salt in large part enters the blood, or rather disappears from the alimentary canal immediately after its ingestion. If it were

present in the blood, we would expect that during this period there would be more of the salt or the acid in the urine than at a later period when the salt returns to the alimentary canal. The rate of the elimination of the salt in the present experiment exhibits no evidence of the blood being richly charged with the salt during the first one or two hours after the administration of the purge.

The next two experiments are similar to the B. part of the preceding in their arrangement, excepting that the salt administered was the sulphate of magnesia, and that the half-hourly excretion of urea and chlorides was carefully ascertained, the former as representing the organic, the latter as representing the inorganic, matter of the urine; the rate, also, of the elimination of the base of the purgative salt, as well as that of the acid, was investigated. In the one experiment a highly-concentrated solution of the salt was taken, in the other a dilute solution, although not so dilute as in Experiment CXV. In the latter of the two experiments the degree of the acidity of the urine was observed. The results of these experiments are arranged in a tabular form.

The urea was estimated by means of the nitrogen or hypobromite process, and the chlorides by the usual volumetric method with nitrate of silver. The magnesia was separated in the form of the ammonio-phosphate, the urine having been previously deprived of its iron and its lime by first acidulating it with hydrochloric acid, then almost neutralising it with carbonate of soda, afterwards adding acetate of soda, and boiling and filtering, and, finally, treating the filtrate with oxalate of ammonia, and, after allowing it to stand for twelve hours, again filtering. The ammonio-phosphate was heated to redness, and the pyro-phosphate obtained, which was the salt weighed. The standard solution of caustic potash employed for the determination of the acidity of the urine contained 0·58 grms. in 100 c.c. of water. As the quantity of the chlorides and urea secreted in a given period depends very largely on the amount of the urine, I have thought it desirable to give the quantity of each in 5 c.c. of urine, as well as the absolute quantity excreted in the course of the half hour. The estimation of the chlorides and of the urea were not continued after dinner, as the food considerably affects their elimination.

The rate of elimination of the chlorides and urea in the normal urine was found to exhibit, as is well known, an increase for a few hours after breakfast, as, indeed, after every meal, and afterwards to undergo with occasional variations a continuous decrease. The decrease was more marked in the case of the chlorides than of the urea.

Experiment CXVI.

Time of Evacuation of Bladder.	Quantity of Urine.		Urea.		Chlorides estimated as NaCl.		Sulphates estimated as		Magnesia estimated as	
	At each Evacuation.	Rate per half-hour.	In 5 c.c. of Urine.	Per half-hour.	In 5 c.c.	Per half-hour.	SO_3. Per half-hour.	$MgSO_4.7H_2O$. Per half-hour.	MgO. Per half-hour.	$MgSO_4.7H_2O$. Per half-hour.
	c.c.	c.c.	m.grms.	m.grms.	m.grms.	m.grms.	grms.	grms.	grms.	grms.
6.30 P.M.	...	...	...	...	...	...	...	...	...	...
8.30 A.M.	640	30	...	...	...	...	...	...	...	...
[8.45 ,,]	Breakfast.		...	...	...	...	...	...	...	...
10.30 ,,	83	20·7	94	389	64	265	...	...	...	...
11.30 ,,	50	25	103	515	75	375				
12.30 P.M.	54	27	92	496	76	410	0·0374	0·1150	0·0033	0·0205
[12.32 ,,]	Administered 20 grammes of sulphate of magnesia dissolved in 20 c.c. of water.								...	...
1 ,,	31	31	90	558	79	489	0·0436	0·1341		
1.30 ,,	23	23	88	403	75	345	0·0436	0·1341		
2 ,,	21	21	93	390	76	319	0·0606	0·1862		
2.30 ,,	20	20	96	384	74	296	0·0563	0·1729	0·0074	0·0458
3 ,,	20	20	98	390	72	288	0·0567	0·1744		
3.30 ,,	20	20	98	390	72	288	0·0755	0·2321		
4 ,,	19	19	98	372	72	274				
4.30 ,,	18	18	98	352	72	260	0·0793	0·2440		
[5.30 ,,]	Dinner.	...	...	...	...	...	...	...	0·0069	0·0424
6.30 ,,	100	25	86	430	73	365	0·1000	0·3075		
8.30 A.M.	904	32·3	...	...	...	...	0·0880	0·2706	0·0064	0·0377
[8.40 ,,]	Breakfast.		...	...	...	...	...	...	...	...
12.30 ,,	196	24·5	...	...	...	...	0.0718	0·2209	0·0051	0·0313
5.30 ,,	220	27·5	...	...	...	...	0·0632	0·1945	0·0031	0·0191

Experiment CXVII.

Time of Evacuation of Bladder.	Quantity of Urine.		Acidity of Urine per half-hour.	Urea.		Chlorides estimated as NaCl.		Sulphates estimated as		Magnesia estimated as	
	At each Evacuation.	Rate per half-hour.	Quantity of S.S. of KHO required for neutralisation	In 5 c.c.	Per half-hour.	In 5 c.c.	Per half-hour.	SO_3. Per half-hour.	$MgSO_4.7H_2O$. Per half-hour.	MgO. Per half-hour.	$MgSO_4.7H_2O$. Per half-hour.
	c.c.	c.c.	c.c.	m.grms.	m.grms.	m.grms.	m.grms.	grms.	grms.	grms.	grms.
10.10 A.M.	...	...	...	...	...	...	...	...	...	...	...
10.45 ,,	30	25·7	(alkaline)	...	...	...	...	...	...	...	...
11.15 ,,	35	35	(acid)	102	720	56	392	0·0361	0·1109	0·0030	0·0184
12.15 P.M.	84	42	4·8	65	551	43	361	0·0355	0·1092	0·0029	0·0181
12.16 ,,	Administered 15 grammes of sulphate of magnesia, dissolved in 250 c.c. of water.										
12.45 ,,	90	90	6·5	34	623	21	378	0·0441	0·1357	0·0061	0·0378
1.15 ,,	90	90	8·5	28	522	16	288	0·0571	0·1756	0·0046	0·0283
1.45 ,,	29	29	8·0	58	341	35	203	0·0606	0·1862	0·0054	0·0332
2.20 ,,	25·5	22	9·9	67	298	39	175	0·0629	0·1936	0·0050	0·0307
2.45 ,,	12·5	15	8·6	50	151	31	93	0·0396	0·1217	0·0047	0·0290
3.15 ,,	17	17	8·6	60	203	42	143	0·0701	0·2157	0·0046	0·0285
3.45 ,,	16·5	16·5	8·8	66	218	...	...	0·0584	0·1795	0·0060	0·0371
4.15 ,,	17	17	9·0	64	218	...	...	0·0556	0·1712		
4.45 ,,	17·5	17·5	9·7	64	225	...	..	0·0616	0·1894	0·0042	0·0261
5.15 ,,	15	15	8·6	58	174	41	123	0·0562	0·1729		
6.15 ,,	31	15·5	8·7	119	368	59	183	0·0673	0·2071	0·0060	0·0371
7.15 ,,	26·5	13·25	...	119	316	64	169	0·0797	0·2452		

The rate of their elimination did not exhibit a substantial difference from that shown in Experiment CXVI. after the administration of the salt, and, as it varied somewhat from day to day, I have not deemed necessary, for the sake of comparison, to insert the results I obtained.

If a careful survey be made of the results of these two experiments it will be seen, first, as regards the rate of the secretion of the urine, that the administration of the concentrated purge has not been followed by an immediate lowering of the rate, as I have sometimes observed to occur; and that an hour after the diluted salt was taken the secretion has become considerably increased. The further course of the rate of the secretion is much alike in both.

Next, as concerns the acidity of the urine, it becomes distinctly increased after the administration of the salt, but this increase is probably for the most part physiological, and would have taken place although the salt had not been administered, as the urine, which is alkaline whilst gastric digestion is actively going on, gradually becomes acid afterwards, and the salt was probably taken whilst the natural acidity was still on the increase. At any rate, I have several times observed that the normal acidity of the urine, some hours after breakfast, is quite equal to that recorded as occurring after the administration of the salt.

The effect of the salt on the amount of the urea is not well pronounced, and it is extremely difficult to rightly interpret the results obtained, owing to the amount of the urea being greatly affected by the quantity of the urinary secretion. From a careful consideration of these results, and attaching more importance to the percentage than to the absolute amount of urea, particularly where the rate of the urinary secretion has become tolerably uniform, as from 1.30 to 3.30 P.M. in Experiment CXVI., and remembering that the urea normally begins steadily to decrease some hours after a meal and when no excercise is being taken, I am inclined to believe that there is a very slight increase in the excretion of the urea, and that, therefore, the salt promotes to a small extent the tissue-metamorphosis of the body. This is, however, at best, extremely doubtful, and does not receive much support in the next two experiments.

The chlorides of the urine are also evidently not much altered

in quantity, if allowance be made for the gradual diminution in their excretion, which begins after digestion has been completed. If altered they are probably slightly diminished. The estimations of the chlorides awanting in Experiment CXVII. are due to the urine having had hydrochloric acid accidentally added to it.

The most interesting, because, to a large extent, the most definite, of the results of the analyses of the urine in these experiments are those which exhibit the rate of elimination of the acid and base of the purgative salt by the kidneys. This is best shown in the following table, where the excess of the

Exhibiting the Excess of the Acid and Base of the Purgative Salt Eliminated in the Urine.

<table>
<tr><th colspan="3">Experiment CXVI.</th><th colspan="3">Experiment CXVII.</th></tr>
<tr><th rowspan="2">Time of Evacuation of Bladder.</th><th colspan="2">Half-hourly Excess, calculated as $MgSO_4.7H_2O$, of</th><th rowspan="2">Time of Evacuation of Bladder.</th><th colspan="2">Half-hourly Excess, calculated as $MgSO_4.7H_2O$, of</th></tr>
<tr><th>Sulphuric Acid.</th><th>Magnesia.</th><th>Sulphuric Acid.</th><th>Magnesia.</th></tr>
<tr><td></td><td>grms.</td><td>grms.</td><td></td><td>grms.</td><td>grms.</td></tr>
<tr><td>12.32 P.M.</td><td colspan="2">Salt administered.</td><td>12.16 A.M.</td><td colspan="2">Salt administered.</td></tr>
<tr><td>1 ,,</td><td>0·0191</td><td rowspan="6">0·0253</td><td>12.45 ,,</td><td>0·0257</td><td>0·0195</td></tr>
<tr><td>1.30 ,,</td><td>0·0191</td><td>1.15 ,,</td><td>0·0656</td><td>0·0100</td></tr>
<tr><td>2 ,,</td><td>0·0712</td><td>1.45 ,,</td><td>0·0762</td><td>0·0149</td></tr>
<tr><td>2.30 ,,</td><td>0·0579</td><td>2.20 ,,</td><td>0·0836</td><td>0·0124</td></tr>
<tr><td>3 ,,</td><td>0·0594</td><td>2.45 ,,</td><td>0·0117</td><td>0·0107</td></tr>
<tr><td>3.30 ,,</td><td>0·1171</td><td>3.15 ,,</td><td>0·1057</td><td>0·0102</td></tr>
<tr><td>4.30 ,,</td><td>0·1290</td><td rowspan="2">0·0219</td><td>3.45 ,,</td><td>0·0695</td><td rowspan="2">0·0188</td></tr>
<tr><td>6.30 ,,</td><td>0·1925</td><td>4.15 ,,</td><td>0·0612</td></tr>
<tr><td>8.30 A.M.</td><td>0·1556</td><td>0·0172</td><td>4.45 ,,</td><td>0·0794</td><td rowspan="2">0·0078</td></tr>
<tr><td>12.30 P.M.</td><td>0·1059</td><td>0·0108</td><td>5.15 ,,</td><td>0·0629</td></tr>
<tr><td>5.30 ,,</td><td>0·0795</td><td>0·0000</td><td>6.15 ,,</td><td>0·0971</td><td rowspan="2">0·0188</td></tr>
<tr><td></td><td></td><td></td><td>7.15 ,,</td><td>0·1352</td></tr>
<tr><td>Total Excess in 17 hours.</td><td>7·3708</td><td>0·8074</td><td>Total Excess in 7 hours.</td><td>1·1061</td><td>0·2061</td></tr>
</table>

magnesia and the sulphuric acid beyond the quantity normally present in the urine is represented. The normal quantity of each was ascertained from an estimation of its amount in the urine secreted previous to commencing the experiment; and, although the urine examined was collected only during two hours, or a little less, the quantity of magnesia and sulphuric acid obtained from it was found by comparison with analyses of

the total twenty-four hours' urine to represent almost exactly the proportion that these other analyses would have led us to expect.

The rate of the elimination of the acid after it has been fairly established, that is, within an hour, or an hour and a half, after the administration of the salt, remains tolerably uniform for a few hours subsequently, but it gradually increases towards evening, in spite of the quantity of the urinary secretion undergoing a gradual diminution, and remains tolerably high throughout the day. The degree of concentration of the solution of the purgative salt when given, evidently exerts little influence on the rate of the elimination of the acid. The rapidity of the elimination of the base, or the magnesia, was probably also much alike in both experiments, although the results of Experiment CXVI. exhibit a somewhat higher rate than those of the other. The apparent lower rate of the latter is probably due to the errors accompanying the analysis of very small quantities of the urine. In Experiment CXVI., which is more extended than the other, the rate of elimination of the magnesia after the first three or six hours is seen gradually to decline, and terminates evidently some hours previous to the complete elimination of the sulphuric acid. The most noteworthy result, however, is brought out in a comparison of the rates of elimination of the acid and base. The former appears in the urine in much larger quantity than the latter, especially after the first hours following the ingestion of the salt. Estimating both acid and base as $MgSO_4.7H_2O$, the quantity excreted of the former is on an average nearly ten times as great as that of the latter. The salt is evidently split up somewhere in the body, either in the intestinal canal or in the blood, almost for certain in the former. Assuming that the decomposition occurs within the intestines, and some recent experiments of mine—made in continuation of the experiments of Series D., and since these were published—render it almost a certainty, the base remains for the most part within the canal, and is evacuated along with the fæces; whilst a large proportion of the acid passes into the blood, and is excreted by the kidneys.

A *résumé* of these additional experiments to Series D. has been pub-

lished in a recent number of the *British Medical Journal*,[1] in which it will be observed that, by estimating both the acid and the base of the purgative salt recoverable from the intestinal canal, I have found that the base does not undergo the rapid absorption spoken of in the experiments of Series D., in which the acid of the salt was alone estimated. In these later experiments sulphate of magnesia, as well as sulphate of soda, was employed, whereas in my former experiments the latter salt alone was used. With both salts the results are the same ; the magnesia, in the one case, and the soda, in the other, disappears very slowly from the alimentary canal, whilst the acid is rapidly absorbed, and pursues the course already described under Series D. This satisfactorily explains why the sulphate of magnesia does not produce the toxic effect which was seen to result from its injection into the blood. The magnesia never enters the blood in a quantity sufficient to permit of its toxicty becoming developed.

The results of the present experiments are in harmony with those of the experiments I have just alluded to, except that the excessively rapid absorption of the acid which occurs soon after the administration of the salt leaves no trace in the urine of its having taken place ; the elimination of the acid is not greater, indeed, is even less, during the first hour following the ingestion of the salt than it is some hours afterwards, when, according to the experiments of Series D., the acid is returning, or has returned, to the alimentary canal, and when, therefore, there ought to be much less of it in the blood, if it be the blood which stores it during its early rapid absorption.

It would be interesting to inquire in what combination the excess of sulphuric acid appears in the urine. As the acidity of the urine is hardly, if at all, greater than normal, it is not in the form of free acid. Most probably it is as a sulphate of the alkaline metals, particularly of sodium.

The next, and the concluding, experiments of this series were made on two convalescent patients in the Infirmary, whose diet was uniform in kind and quantity from day to day throughout each experiment. The daily supply of liquids was also perfectly definite and equal. The object of these experiments was to ascertain the gross and more extended effect of a dose of a purgative salt on the excretion of the urea and chlorides : in the previous experiments the immediate and detailed effect of the salt on the excretion of these substances was determined.

[1] "On the Absorption of Certain Salts from the Alimentary Canal," No. 1146, p. 1204, Dec. 16, 1882.

Experiment CXVIII.—A. W., male, æt. 38. The urine of the twenty-four hours was collected and measured every morning at six, and the purgative (20 grammes of sulphate of magnesia dissolved in half a tumblerful of water) was administered at that hour on the morning of the third day, or at the commencement of the fourth period of twenty-fours, as represented in the following table :—

Experiment CXVIII.

Period of 24 hours.	Urine.		Urea.		Chlorides, calculated as NaCl.	
	Total Amount.	Specific Gravity.	In 5 c.c. of Urine.	In total Urine.	In 5 c.c. of Urine.	In total Urine.
	c.c.		grms.	grms.	grms.	grms.
I.	1426	1014·2	0·066	18 836	0·045	12·843
II.	1525	1014·5	0·066	20·130	0·046	14·030
III.	1595	1014·3	0·067	21·373	0·042	13·398
	Salt admin	istered.				
IV.	1369	1015·3	0·068	18·618	0·038	10·404
V.	1738	1012·8	0·058	20·160	0·039	13·556
VI.	1025	1014·8	0·064	13·120	0·044	9·020

Experiment CXIX.—J. G., male, æt. 47. All the conditions of this experiment were exactly the same as in the previous experiment.

Experiment CXIX.

Period of 24 hours.	Urine.		Urea.		Chlorides, calculated as NaCl.	
	Total Amount.	Specific Gravity.	In 5 c.c. of Urine.	In total Urine.	In 5 c.c. of Urine.	In total Urine.
	c.c.		grms.	grms.	grms.	grms.
I.	1273	...	...	...	...	...
II.	1267	1017·9	0·078	19·765	0·050	12·670
III.	1353	1016·8	0·084	22·764	0·045	12·195
	Salt admin	istered.				
IV.	1453	1018·0	0·083	24·119	0·037	10·752
V.	1567	1017·7	0·087	27·265	0·049	15·356
VI.	1339	1023·7	0·110	29·458	0·071	19·013

The effect of the purgative on the quantity of the urinary secretion is in accordance with the conclusions derived from my other experiments. The effect on the excretion of the urea is either *nil* or extremely small. The excretion of the chlorides is, on the contrary, considerably modified, being distinctly less during the twenty-fours following the administration of the purgative. The partial disappearance of the chlorides is probably due to the purgative dejection carrying with it a portion of the

chlorides of the body, derived from the blood by means of the intestinal secretion which the cathartic excites.

The experiments of this series are, as I have already said, fragmentary and not numerous enough to warrant definite conclusions, but they render it highly probable that a purgative dose of sulphate of soda or sulphate of magnesia acts as a diuretic as well as a cathartic, the diuretic effect being generally most evident on the day following the administration of the purgative. The action of the salt on the composition of the urine, as tested by the estimation of the urea and the chlorides, is apparently of little moment. Finally, as regards the elimination of the salt itself in the urine, some facts of considerable interest have been elicited, which form a material addition to the results of previous experiments (Series A). Whether the sulphate of soda exhibits the same inequality in the elimination of its acid and base, as the sulphate of magnesia does, I have not yet determined.

CONCLUSION.

It is now desirable that I place together in a readily intelligible form the more important results derived from the numerous experiments which I have made for the purpose of ascertaining more precisely the nature of the action of a saline cathartic. This is the more necessary, as, so far, the results of each series of experiments have been mostly considered by themselves, and not in conjunction with those of the other series.

In my first experiments, it will be remembered that I hoped to prove, and succeeded in proving by the method employed, that the salt does not cause any increase of secretion within the alimentary canal, but hinders the absorption of the fluids in which it is dissolved, being itself slowly diffusible and uniting with and retaining the water. That theory I was compelled to abandon after obtaining the results of the three subsequent series of experiments. The work upon which it was based is not, however, valueless, for, besides being accompanied by certain interesting analyses exhibiting the distribution of the salt in the urinary and fæcal excretions, it has shown that the secretion which the purgative excites is greatly diminished if the blood is previously concentrated; and, indeed, is so much diminished that in most cases purgation does not at all occur.

It therefore rests with me to construct another theory which will meet the requirements of the results of all of the experiments and unite them into a harmonious whole. I shall, for the sake of simplicity and lucidity, consider these results in relation to the following points and in the following order, supplementing them, where necessary, by other experiments.

A. The Effect of the Saline Cathartic on the Alimentary System.

I. Does the salt provoke an increase of secretion within the alimentary canal?

II. The source of the secretion:—

1. Stomach.
2. Liver.
3. Pancreas.
4. Small intestine.
5. Large intestine.

III. The nature and characters of the secretion.

IV. The mode of the production or excitation of the secretion.

V. The action of the salt on the peristaltic movements of the intestines.

B. The Effect of the Saline Cathartic on Other Parts of the Body than the Alimentary System.

I. On the blood and circulation.

II. On the urinary secretion.

A. The Effect of the Saline Cathartic on the Alimentary System.

I. *Does the Salt provoke an increase of Secretion within the Alimentary Canal?*

The experiments of Series B., C., and D. answer this most distinctly in the affirmative. Some objections might be urged against the method employed in Series B., but the methods of Series C. and D. are perfectly unimpeachable; and I claim by these to have completely and satisfactorily demonstrated for the first time that the salt does actually excite secretion. In the experiments of Series B., by using a certain proportion of a 10 per cent. solution of sulphate of soda to a given length of intestine, it was found that a solution of this strength did not increase in bulk. The quantity of solution was, however, probably smaller than what at any moment comes in contact with

the same length of intestine during the action of a purgative dose of the salt, adminstered in the usual manner; for, in Experiments LV. and LVII. (Series C.) and LIX. (Series D.), a 5 per cent. solution appears to be that which neither increases nor diminishes in bulk. But, apart from the increase of the fluids in the alimentary canal, I am satisfied from the alteration in their characters and properties that even the weakest saline solution provokes secretion, although absorption, proceeding at an equal or greater rate, may prevent any increase in the volume of the fluid within the canal.

II. *The Source of the Secretion.*

From what part of the alimentary canal is it derived? Is it from one or other, or a combination, of the various portions of the canal and its attached glands; and, if from a combination of some or all of them, to what extent does each contribute?

1. *Stomach.*—If this organ contains no food, the salt does not remain long within it, probably not over half an hour (Experiments LXII., LXIII., and LXIV.). During this short period a 10 per cent. solution will scarcely increase in bulk (Experiments LXIX. and LXX.), while a 20 per cent. solution may excite a fairly rapid secretion (Experiment LXII.). As the salt is not usually administered in a solution of greater strength than 10 per cent. we may conclude that the purgative extracts but very little fluid from the stomach, and that the secretion excited appears always to possess an alkaline character.

2. *Liver.*—In all the experiments of Series D. the secreted fluid was examined to ascertain if much bile was present, and the fulness or emptiness of the gall-bladder noted. Rutherford[1] has shown that the secretion of the bile is augmented during the action of sulphate of soda, but not during the action of sulphate of magnesia. In most of my experiments with the former salt there was hardly any visible staining of the intestinal fluid with bile, and the gall-bladder was almost invariably well filled; from which I infer that, whatever be the action of the absorbed salt on the secretion of bile by the liver, the discharge of the bile from the gall-bladder into the intestine is little or not at all accelerated by this salt. Even were the discharge increased, it could not add much to the total quantity of fluid within the

[1] Rutherford, *op. cit.*, p. 67.

intestines. For, according to Bidder and Schmidt,[1] the hourly amount of biliary secretion in a cat, 3 kilogrammes in weight, does not exceed 1·8 c.c.; and as in an hour the maximum of the general secretion excited by the purgative has been reached, the bile, allowing for an increase in its discharge, could not contribute more than a very few cubic centimetres of the 40 to 80 c.c. observed to be poured into the intestine during the action of the salt solution (Experiments LX. and LXI.).

3. *Pancreas.*—It is much more difficult to ascertain to what extent this gland adds to the purgative secretion. The pancreatic juice being without colour, its admixture with the purgative fluid cannot be so readily detected as in the case of the bile. Its powerful digestive properties might give a clue to its presence, but as these in their nature are identical with some of the digestive properties of intestinal juice, its presence cannot with certainty be proved, especially if in small quantity. If in large quantity, the difficulty is not so great, for its diastatic and proteolytic powers are very much stronger than those of the intestinal juice. I have compared the diastatic power of the intestinal secretion obtained by the action of the salt within a washed out ligatured loop—and which was, therefore, uncontaminated with pancreatic juice—with the fluid found in the intestines after the action of the salt administered per os. Five cubic centimetres of the former (Experiment XLIX.) produced 0·489 gramme of sugar from a 1 per cent. solution of starch, while the same quantity of the latter (Experiment LXI.) produced 0·662 gramme. Moreover, 5 c.c. of the blood of the cat used in the latter experiment contained sufficient ferment to form 0·411 gramme of sugar from a starch solution. We therefore infer that a saline purgative scarcely, if at all, stimulates the outflow of the pancreatic juice. For, had the fluid of the intestine in Experiment LXI. contained much of this juice, the diastatic power of the fluid would have been very much greater than that represented by the quantity of sugar obtained from the starch digested. The digestion in each case was continued for forty-eight hours. Kroeger[2] found that 1 c.c. of pure pancreatic juice could in the course of half an hour convert 4·67 grammes of starch into

[1] Bidder u. Schmidt, *Die Verdauungssäfte*, &c., Leipzig, 1852, S. 209.

[2] Kroeger, *Hermann's Hdbuch. d. Physiologie*, Bd. v. Th. 1, Maly, S. 195.

sugar, and Roberts, in his *Lectures on the Digestive Ferments*, assigns to the juice an almost incredibly high diastatic power[1]; and there is no reason to believe that the secretion in the cat is not as active as that obtained from other animals. We accordingly conclude that the pancreatic juice shares but very slightly in the increase of the purgative fluid within the alimentary canal, as its presence even in very small quantity would impart a high diastatic power to the purgative secretion. It is but right to mention that Barbier[2] quotes Gendrin as stating that he had experimentally determined that the pancreatic secretion is excited during the action of a purgative. The name of the purgative is not however given.

I might make use of the same form of argument as I have done in the case of the bile to prove that, even were the pancreatic secretion stimulated, the quantity poured out in the course of an hour would be perfectly insignificant compared with the observed increase of the purgative fluid within the intestines during that time. The pancreas of the dog during digestion secretes 0·1 c.c. of juice for each kilogramme of the animal's weight[3]; and if the rate of secretion be similar in the cat, about 0·3 c.c. would be poured out in a cat weighing 3 kilogrammes, and, allowing this to be doubled or even trebled by the action of the purgative, it is evident that the pancreas could not add more than 1 or 2 c.c. to the intestinal contents in the course of an hour.

4. *Small Intestines.*—This viscus appears to be the main source of the fluid. Its capability of furnishing a copious secretion under the action of the salt, many of my direct experiments on the intestines (Series B. and Experiment LXXI.) indubitably prove. It is probable that this secretion is rapidly poured out and that it very quickly passes onwards with the salt to the colon, particularly if the intestine be tolerably free from food (Series D., especially Experiment LXIII.). That the characters of the fluid point to its being derived from the intestine, has already received confirmation in the discussion of the almost passive part which the stomach, liver, and pancreas play in its produc-

[1] Roberts, p. 35.

[2] Barbier, *Traité de matière médicale*, 1830, tom. iii. p. 194.

[3] Bidder u. Schmidt, *op. cit.*

tion, and will be further supported when we pass to the actual consideration of these characters.

5. *Large Intestine.*—It is somewhat difficult to determine with accuracy how much of the fluid is contributed by the large intestine in a case of ordinary purgation. For, by the time that the salt has reached the colon, it has become so diluted by the secretion of the small intestine as no longer to possess its previously active excito-secretory power. But that the large intestine is capable of furnishing a fair amount of secretion, if sufficiently stimulated by a tolerably concentrated solution of the salt, is supported by several of the experiments of Series B. It is possible, indeed highly probable, that, even when the salt reaches the colon in a diluted condition, and when the fluid undergoes no increase within that viscus, there is effected, by an equality of absorption and secretion, a considerable admixture of colic secretion with the purgative fluid.

The general conclusion, therefore, as to the source of the purgative fluid, is that it is mainly derived from the intestines, and particularly from the small intestine; the stomach, liver, and pancreas supplying under ordinary conditions very little or practically none of the fluid.

III. *The Nature and Characters of the Secretion.*

If it is granted that the secretion excited by the presence of the salt is derived almost entirely from the mucous membrane of the small intestine, it still remains to be decided what is the nature of the secretion. Among those who admit that the purgative does excite secretion there is much difference of opinion as to this, some maintaining that it is a true succus entericus, others that it is an exudation, and others that it is a transudation. Before proceeding to determine to which of these forms of secretion the purgative fluid is by its characters most closely allied, it will be well to briefly define what we understand by each of these varieties of secretion.

An exudation is a fluid which is poured out by the vessels of a tissue in a state of inflammation produced by irritation or otherwise. Of all the fluids met with in the body and outside the blood and lymph vessels, it is that which most approaches in composition the blood-serum; and, like the serum, it contains a large amount of organic matter, particularly of coagulable

albumen, and it abounds also in leucocytes. Further, the inflamed condition of the tissue producing the exudation is generally evidenced by the unusual distension of its blood-vessels, and consequent redness.

The term transudation is often indifferently applied to an inflammatory or a dropsical effusion. Here, however, we shall use it in its stricter sense, and apply it only to a fluid possessing a dropsical character, which may be, and most commonly is, secreted independent of any inflammation of the organ or tissue from which it proceeds, and is generally the result of changes in the pressure or composition of the blood.

The transudation resembles the exudation qualitatively in its composition, but contains much less organic matter. Both fluids yield a very distinct coagulum of albumen when heated, especially the exudation. Apart from the circumstances which occasion their production, and which are often difficult to determine, the exudation and the transudation are mainly to be distinguished from each other by the difference in the quantity of organic matter they contain. And it is relying upon this difference, and on the presence or absence of inflammation of the intestinal mucous membrane, that certain previous observers have regarded the purgative secretion as being of the nature of an exudation or of a transudation.

The succus entericus, or intestinal juice, is a secretion whose characters are very imperfectly known. This arises from the great difficulty experienced in obtaining it pure and in sufficient quantity to permit of its analysis. Thiry gives an analysis [1] of some juice obtained by prolonged mechanical stimulation of an intestinal fistula, made by an operation which I have already described;[2] but as the fistula behaved towards purgative salts in a manner contrary to what we now know to be natural, we may conclude that the secretion thus obtained was as much an exudation from irritation as a true intestinal juice, and its chemical composition supports this view. Moreau procured a copious secretion from a loop of the intestines after complete division of its mesenteric nerves, and notwithstanding Vulpian's objections, it is probable from various reasons, some of which I

[1] Hoppe-Seyler's *Physiologische Chemie*, S. 273.

[2] *Supra*, p. 8.

have already given, that this secretion is a true succus entericus,[1] and not a mere exudation or transudation. This opinion has quite recently received support in a paper on intestinal digestion by Dr. Meade Smith.[2] Dr. Smith, by establishing a permanent fistula in the lower part of the duodenum of a dog, and inserting into it an ordinary Bernard gastric cannula, and by occluding the intestine a few inches above and below the fistula by means of two distended india-rubber balls, has, after washing out the portion of gut between the balls, obtained as much as 20 to 40 c.c. of secretion from 12 inches of intestine, and that without the application of stimulation. The secretion thus obtained possesses almost exactly the same composition as that of Moreau. The most remarkable feature of intestinal secretion is that it contains a very small quantity of organic matter—in Moreau's secretion, 0·39 per cent., and in Smith's secretion, 0·54 per cent. We may, therefore, with tolerable safety conclude, in spite of the observations of Thiry and others, that a very small percentage of organic matter is a constant character of intestinal juice. It is upon this distinction that I shall mainly rely for the determination of the nature of the purgative secretion.

Certain other characters have been ascribed to intestinal juice, which ought to help us to distinguish it from an exudation or a transudation. It is said to be able to digest starch, invert sugar emulsify fat and peptonise albumen. Much variety of opinion however, exists as to its having any or all of these properties. I shall immediately consider to what extent these properties are possessed by the purgative fluid.

With the object of facilitating the comparison of the purgative

	Exudation.[3]	Peritoneal Transudation.[4]	Succus Entericus.	
			Moreau.[5]	Smith.
Percentage of Solids,	8·15	3·03	1·34	1·14
Organic, . .	7·25	1·92	0·39	0·54
Inorganic, . .	0·90	0·79	0·95	0·60

secretion with the exudation, transudation, and intestinal juice, I have thought it desirable to give a precise statement of the

[1] *Supra*, pp. 5 and 6.

[2] Meade Smith, *Medical News*, Philad., April 15, 1882.

[3] Hoppe-Seyler's *Physiologische Chemie*, S. 610.

[4] *Ibid.*, S. 603.

[5] *Ibid.*, S. 272.

percentage of solids in the latter, especially of the organic matter, which consists mainly of albumen.

An acute exudation hardly differs in composition from blood-serum, and varies extremely little with the locality of the body in which it occurs. It is otherwise with the transudation, as the quantity of its organic matter depends largely on the situation of the transudation, being sometimes a little less, but generally much greater, than that contained in a peritoneal transudation, which, in the absence of any analysis of a transudation from a mucous membrane, I have selected partly from its proximity to the intestines, and partly from its representing the class of transudates with a small percentage of organic matter, as offering the only possible standard of comparison for the purgative secretion.

If a comparison be now instituted between these various secretions and the purgative fluid, it will be found that the latter most nearly agrees in composition with the intestinal juice of Moreau or Smith. For, although I very frequently examined it for albumen, I never found more than the merest trace (B. Series of Experiments), as indicated by a *faint* opalescence on acidification and heating, or by the application of other tests for albumen. I regret that it has been impossible to procure exact quantitative analyses of the purgative secretion, as the presence of the purgative salt and of epithelial débris from the intestinal mucous membrane interfered with an accurate determination of the organic and inorganic solids. The quantity of the salt was very large in proportion to the solids of the secretion, and after the evaporation of the fluid it was impossible to be certain that the sulphate of soda, the salt generally employed, and which contains a large quantity of water of crystallisation, was present in its usual form, and not to any extent decomposed, or crystallised with less water. For, from the weight of this residue and of its ash after burning, and from the estimation of the sulphate of soda present, had to be determined the amount of organic matter. Notwithstanding these difficulties, I did on one occasion attempt a quantitative analysis of the fluid obtained from the action of 10 c.c. of a 20 per cent. solution of the salt in a previously well-washed loop of the small intestine, 60 c.m. in length. The cat was killed after three hours, and the fluid

measured 89 c.c. The fluid was filtered to remove from it as well as possible the epithelial débris, and was then evaporated to dryness, the residue weighing 3·225 grammes. The weight of the crystalline sulphate of soda recovered was 1·562 grammes, which, after deduction from the total residue, leaves 1·663 grammes, or the amount of solids present in the purgative secretion. Of these solids 0·810 gramme was inorganic, and and 0·853 organic. The percentage, therefore, of organic matter, although higher than that of the succus entericus, was not nearly so great as that of an exudation, and was considerably less than that of a transudation. A portion of the organic matter was doubtless composed of the finer epithelial débris which might readily have passed through the filter.

As the percentage of inorganic matter in the exudation, transudation and enteric juice is practically the same for all, its percentage in the purgative fluid can afford no help in determining the nature of the fluid. Apart from such an object, it is remarkable, however, that the purgative dejections contained a large proportion of ash, as is apparent from the analyses accompanying the experiments of Series A. and some of Series D. (LIX. and LXVI.); and the larger the interval between the administration of the salt and the occurrence of purgation the greater appears to be the percentage of ash (Experiment XXIII. and p. 39).

The large quantity of inorganic matter is probably not due to the secretion, as it is poured out from the intestinal mucous membrane, containing a larger percentage of salts than the blood, but to the condensation, so to speak, of the secreted fluid in the lower part of the intestines by the absorption of its water at a greater rate than of its dissolved salts, in the manner I have already explained in connection with the return of the acid of the purgative salt to the alimentary canal. Whatever be the exact nature of the phenomena involved, we are not warranted in assuming that the poured-out secretion is excessively rich in saline matter, for no secretion contains a larger percentage of salts than the blood from which it is primarily derived. The urine is an exception, but the structural conditions of the secreting organ account for its occupying an anomalous position

Besides the small amount of albumen or organic matter in the purgative secretion, which has been as yet the principal reason advanced for regarding the secretion as consisting of intestinal juice, there is also the presence, frequently in large quantity, of mucus, a substance which one would be more likely to find in a physiological secretion than in an inflammatory exudation. I have more than once in the course of this communication insisted upon this fact as testifying to the true secretory character of the purgative fluid. I do not, however, wish to present this point strongly, as I believe that the mucus forms no essential part of the secretion from the Lieberkühnian follicles, but is produced, in all probability, most largely from the superficial epthelium of the mucous membrane. Moreau's secretion possessed extremely little viscosity.

Another most important fact, and one which strongly weighs against the exudative character of the fluid, is the absence of any trace of inflammation in the intestinal mucous membrane. Many previous observers, particularly Vulpian, have maintained that the salt excites inflammation of the intestinal mucous membrane. But this result they obtained from the injection of a saturated solution of the cathartic into an intestinal loop, an experiment which does not represent what naturally occurs when the purgative is administered per os. Weaker solutions, even a 20 per cent. solution, as my numerous experiments almost without exception prove, never cause the slightest visible redness or inflammation of the intestine.

The microscopical characters of the purgative fluid do not help us much in deciding as to its nature. The fluid usually contained a number of colourless corpuscles, and in some instances they were tolerably abundant, especially in the mucous deposit. If these are to be regarded as leucocytes or lymph-corpuscles, their presence is indicative of the inflammatory character of the fluid. But more probably they are mucous corpuscles; and it may be that they are formed from the protoplasmic contents of the epithelial cells of the villi, which I have generally observed, by microscopical examination, to become goblet-shaped and partially empty after the action of the salt.

I now proceed to consider what evidence there is of the

purgative secretion being a true succus entericus from an examination of its digestive properties. This is a matter of some difficulty for the pharmacologist, as the physiologist has not as yet precisely defined the extent and even the nature of these properties. The more recent investigators assign to it the power of converting starch into sugar, cane-sugar into grape-sugar, and, doubtfully, albumen into peptones, and fat into fatty acids and glycerine; but none of them has attempted to fix the limit of these powers, a point most essential in ascertaining whether or not the purgative secretion consists entirely of intestinal juice or is a mixture of the juice with a large proportion of exudation or transudation. In both cases the fluid would digest starch and sugar, but in the former more powerfully than in the latter. As it is difficult to conceive of even a purely inflammatory exudation from a secreting membrane being unmixed to some extent with the natural secretion of the membrane, a mere qualitative proof of the digestive power of the fluid is of no value; it is necessary also to know the limit of this power. In order, therefore, to provide myself with some data of the absolute strength, as well as of the exact nature of the digestive action of the normal intestinal juice, I made infusions of well-washed intestinal mucous membrane, since it was difficult to obtain the juice itself by ordinary stimulation of the living intestine. Infusions of secreting organs, if not made too dilute, are well known to be often quite as active as the usual secretion of the organ. I also prepared infusions of other tissues and organs of the body, and compared their activity with that of the intestine. Several extensive experiments of this kind were made. The tissue or organ was removed from a fasting animal immediately after being bled to death; it was at once weighed and cut up into minute pieces, and infused for twenty-four hours in four times its weight of a 1 per cent. solution of chloride of sodium. Five c.c. of the infusion were mixed with 10 c.c. of a 1 per cent. solution of starch, and another 5 c.c. with 10 c.c. of a 1 per cent. solution of cane-sugar, all of which were previously ascertained to contain no glucose. The mixed fluids were placed in an oven at a temperature of 35–40° C., and the first apperance of glucose was ascertained by repeated testing with Fehling's solution. To ensure

accuracy many little precautions were necessary which it is needless to detail. Sometimes 5 c.c. of the infusion were mixed with 100 c.c. of a 1 per cent., or with 50 c.c. of a 2 per cent. solution of starch or cane-sugar, and allowed to digest for forty-eight hours, when the amount of digested starch or sugar was quantitatively determined. The animals used were the cat, dog, and rabbit. I shall confine myself for the present to a statement of the results of my experiments with the first of these.

Tissue or Organ infused.	Experiment CXX.			Experiment CXXI.	
	Time in which Glucose appeared in		Amount of Sugar obtained from Starch.[3]	Time in which Glucose appeared in	
	Starch Solution.[1]	Cane-Sugar Solution.[2]		Starch Solution.[1]	Cane-Sugar Solution.[2]
	h. m.	h. m.	grms.	h. m.	h. m.
Duodenum,	2 15	never appeared	0·047	1 45	2 30
Jejunum,	2 30	1 45	0·031	2 0	2 30
Ileum,	3 0	12 20	0·019	2 0	4 0
Colon,	2 45	never appeared	0·032	2 30	never appeared
Œsophagus,	3 0	,,	0·012	...	...
Stomach,	3 0	,,	0·018	2 15	never appeared
Pancreas,	at once	,,	0·882[4]	at once	,,
Muscle,	3 45	,,	0·020	...	...
Blood-serum,[5]	3 0	,,	0·035	2 30	never appeared

From these and other experiments I have concluded that the only ferment peculiar to the small intestine is the cane-sugar ferment or the "ferment inversif" of Bernard, and that the intestines do not contain more of the diastatic ferment than is to be found in the tissues and fluids of the body generally. The apparent greater activity which the duodenum exhibits is due to

[1] Five c.c. of infusion mixed with 10 c.c. of 1 per cent. solution of starch.

[2] Five c.c. of infusion mixed with 10 c.c. of 1 per cent. solution of cane-sugar.

[3] Five c.c. of infusion mixed with 50 c.c. of 1 per cent. solution of starch, allowed to digest for forty-eight hours.

[4] Gave no blue colour with iodine.

[5] The serum was, previous to measuring the 5 c.c., diluted with four times its bulk of water.

the presence of a small quantity of pancreatic secretion which has soaked into the mucous membrane, and which the washing has failed to remove. If the intestinal juice contain more diastatic ferment than these experiments indicate, it must be formed in the glands at the moment of its secretion, and cannot be stored up to any extent as are the ferments of the pancreatic, salivary, and gastric glands. But I do not believe that the intestinal glands are exceptional in this respect. The intestinal juice, therefore, is probably not richer than serum in the starch-digesting ferment. The presence, accordingly, of this ferment in the purgative secretion is no proof of the fluid being the intestinal juice and not an exudation or transudation.

Although it would thus appear that an examination of the digestive powers of the purgative secretion, particularly of its diastatic action, will help but little to decide what the nature of the secretion is, yet it will not be altogether uninteresting to consider the results of such an examination. I have tested the digestive powers of a very large number of the purgative secretions. Only those results are of value where the intestine, previous to injecting the salt, has been well washed out, so as to remove every trace of the pancreatic and other secretions. This, however, it is difficult to accomplish thoroughly, as prolonged or vigorous washing is apt to injure the mucous lining of the living intestine. It is to be expected, therefore, that the diastatic action of the purgative secretion will have its power increased by the presence of a trace of pancreatic juice, and that the succus entericus poured out as a consequence of the stimulation of the cathartic, will appear to possess a more powerful diastatic action than the two last experiments might lead us to anticipate. And that this is so the subjoined experiments prove. The proportion of the inversive ferment present is, however, much the same as it was in the infusion of the normal mucous membrane.

The fluids (4) and (5) were both obtained from different loops of the small intestine of the same cat, the former after the action of a 20 per cent. solution of sulphate of soda, the latter after an equally strong solution of chloride of sodium. The mucous membrane of the chloride of sodium loop was much inflamed, and the fluid contained a considerable quantity of albumen. Fluid (6) was obtained by the injection of a 20 per cent

solution of phosphate of soda, and (7) by the injection of a 20 per cent. solution of sulphate of magnesia. In the first three experiments sulphate of soda was employed, and, in all, the method of the application of the salt was that of Colin and Moreau.

No. of Experiment.	Part of Intestine from which Purgative Secretion was obtained.	Digestion of Starch.		Digestion of Cane-Sugar.	
		Time in which Maltose appeared.[1]	Amount of Maltose formed after 48 hours.[2]	Time in which Invert-Sugar appeared.[3]	Amount of Invert-Sugar formed in 48 hours.[4]
		h. m.	grms.	h. m.	grms.
1. (XLVII.)	Ileum	0 30	0·128	6 0	0·081
2. (XLIX.)	,,	0 15	0·489[5]	...	0·093
3. (LII.)	,,	0 30	...	1 0	...
4. ...	Jejunum	0 10	...	2 15	...
5. ...	,,	0 15	0·192	2 15	0·076
6. ...	,,	0 10	...	0 35	...
7. ...	Ileum	1 30	0·097	2 15	0·189

The secretion provoked within the small intestine by the presence of a saline purgative, contains, therefore, very little of either the amylolytic or the inversive ferment, but probably as much of each as the true intestinal juice would appear to possess, if the digestive powers of a strong infusion of the intestinal mucous membrane may be regarded as fairly representing the digestive activity of the juice itself.

While the comparison I have instituted between the digestive powers of the purgative secretion and those of the intestinal juice offers little or no positive evidence of the former consisting of the latter, yet it presents no objection to the acceptance of this opinion. It is to be remarked that blood-serum contains as much diastatic ferment as the intestinal mucous membrane, and it is probable that an inflammatory exudation will contain as much of the ferment as the serum, from which it is so immediately derived. Accordingly, it must be conceded in support of Vulpian's view, that, were the purgative secretion an exudation

[1] Five c.c. of purgative fluid mixed with 10 c.c. of 1 per cent. solution of starch.

[2] Five c.c. of purgative fluid mixed with 100 c.c. of 1 per cent. solution of starch.

[3] Five c.c. of purgative fluid mixed with 10 c.c. of 1 per cent. solution of cane-sugar.

[4] Five c.c. of purgative fluid mixed with 100 c.c. of 1 per cent. solution of cane-sugar.

[5] Deep blue with iodine at end of forty-eight hours.

instead of true intestinal juice, its diastatic power would be as high as it was actually found to be.

In the protocols of some of the experiments of Series B. and of Series D., there exist some estimations of the fat- and albumen-digesting powers of the purgative fluid, which show that these powers are scarcely, if at all, possessed by the fluid; neither have they been ascribed to the succus entericus, or, if so, only to a very limited extent. Indeed, it is highly probable that the succus entericus is a secretion which, physiologically, is of most service as a solvent and diluent of the food that has already been digested by the action of the gastric, pancreatic, and biliary ferments, and that its digestive function is of the smallest importance, unless for the conversion of cane into grape sugar, the ferment for effecting this change existing nowhere else in the body.

Taking into consideration the various characters, chemical, microscopical, and digestive, of the purgative secretion, which I have given in detail, and remembering that the intestinal mucous membrane presents no trace of inflammation from the action of the salt, the conclusion which I have arrived at is that the secretion is mainly obtained from the follicular glands of the intestines, and is, therefore, for the most part a true intestinal juice. It contains too little albumen, and there is no evidence of inflammation to constitute it an exudation. And it can hardly be regarded as a transudation, even were its characters not other than those which an intestinal transudate might possess; for the conditions which occasion a transudation in the body are always associated with a decided alteration of the composition or pressure of the blood, which alteration cannot be proved to occur after the administration of a saline cathartic, to the extent of causing a rapid localised intestinal transudation.

IV. *The Mode of the Production or Excitation of the Secretion.*

This depends considerably on what the nature of the secretion is admitted to be. If it be an inflammatory exudation, as Vulpian seems inclined to hold, then it is produced by the salt irritating and dilating the superficial vessels of the intestinal mucous membrane, causing a stasis of the blood-

current, and an outpouring of serum. This would equally well happen were the salt applied to a mucous membrane devoid of special glands. But I have just stated my reasons for believing that such an inflammatory irritation does not occur.

If, as Schmidt and a few others have suggested, the fluid be a transudation, we must suppose that the salt affects the composition or pressure of the blood so as to allow of a modified serum being transuded through the walls of the blood-vessels of the intestinal mucous membrane. Such an alteration of the blood I have already said does not occur. And, were the transudation the result of the action of the salt on the blood, we would expect purgation to be the most active after the direct injection of the salt into the blood, whereas the experiments of Series E. have distinctly proved that the salt possesses no cathartic action whatever when so injected. But although the purgative secretion cannot therefore be a transudation resulting from the action of the salt on the blood, it may be urged that it is a transudation proceeding from the salt effecting certain peculiar changes in the vessels and epithelial covering of the intestinal mucous membrane. It is very difficult, however, to conceive of such changes, and there is no proof whatever of their occurrence. There is yet another possible method by which the purgative secretion may be a transudation, and which does not necessarily involve any alteration of the structure or function of the intestinal lining. I refer to osmosis, the probability of whose occurrence was first maintained by Liebig and Poiseuille, and afterwards by Funke, Heidenhain, and others. These observers evidently supposed that, with the vessel wall and the intestinal epithelium and the intervening tissue, all acting as a septum, the osmotic power of the salt could come into play and abstract from the blood a fluid or secretion having the characters of a transudate. It is, however, highly improbable that such a septum as this, formed of living tissues, can behave towards saline solutions in the same manner as a septum of parchment or dried bladder. At any rate, I have been able to prove to my satisfaction that the purgative secretion is not the result of the endosmotic action of the salt. What this proof consists of, I shall come to immediately. In the meantime, holding it as

established that the purgative secretion is neither an exudation nor a transudation, but consists of intestinal juice, I shall endeavour to elucidate how the stimulation of the Liberkühnian glands is effected by the salt.

The salt may excite the activity of the secreting cells of the follicular glands of the intestines, either by coming directly into contact with the cells, or by acting on them reflexly through the agency of the intra-intestinal nerves. Owing to the cells being deeply situated within the gland, and removed from contact with the contents of the intestine, it is not likely that the salt acts directly on the cells. Even were it supposed that the salt could diffuse into the cavity of the gland and thus reach the cells, it could hardly reach the cells more readily than if it had been injected into the blood. For, dissolved in the blood, it would, by means of the blood-vessels of the intestinal mucosa, be brought into the closest proximity to the glandular cells. Yet, as I have frequently had occasion to mention, the salt, although injected into the blood in large quantity, does not excite a drop of intestinal secretion. As little, therefore, may the salt stimulate the secreting cells when it reaches them, and necessarily in a state of dilution, by direct diffusion from the lumen of the intestine. A saline cathartic evidently possesses no special excito-secretory power over the glands of the intestine, such as is well known to be possessed by many other substances, as pilocarpin, the salts of arsenic, antimony, mercury, iron, tin, &c., all of which excite intestinal secretion even when injected into the blood. The saline cathartic, therefore, would appear to stimulate the glands reflexly, by producing a certain impression on the sensory nerves terminating in the surface of the mucous membrane of the intestine, which impression, conveyed, probably through Meissner's plexus, to the secretory cells of the gland, excites them to action; just as certain sapid and other substances can stimulate the salivary glands when brought into contact with the mucous membrane of the mouth.

Besides direct or indirect excitation of the glands, there is yet another way in which it is possible for the salt to abstract secretion from the glands. I once more allude to osmosis. This implies that the salt penetrates the cavity of the gland and establishes osmotic relations with the contents of the secreting

cells, which, as they part with their fluid to the salt, have their fluidity restored by an absorption of liquid from the blood. I have already expressed the opinion that the salt does not penetrate freely into the cavity of the gland, and certainly not in a state of concentration sufficient to exert an appreciable osmotic effect on the secretory cells.

If, then, it be maintained that the secretion excited by the salt is for the most part intestinal juice, and that the outpouring of the juice is the consequence of a reflex stimulation of the glands by the salt applied to the surface of the mucous membrane, it behoves us in the next place to inquire what are the properties possessed by cathartic salts which enable them thus to act, and otherwise to cause purgation.

The group of the saline cathartics consists, as is well known, of certain of the compounds of the alkalies and alkaline earths (usually potash, soda, and magnesia), with mineral and organic acids devoid of intrinsic poisonous action, as sulphuric, phosphoric, tartaric, and citric acids. Indeed, it may be broadly stated that any saline compound, whose acid or base does not possess a strongly specific action, will, if the dose be large enough, produce purgation. But, although the number of possible saline cathartics is thus large, and might include amongst others the alkaline chlorides, nitrates, and acetates, yet the application of the name saline cathartic is restricted in ordinary usage to a few salts, which by experience have been found to purge in a moderate dose and unattended by any disagreeable manifestation of the specific action of the metal or acid of the salt. These salts are the sulphate of soda, sulphate of magnesia, sulphate of potash, phosphate of soda, tartrate and bitartrate of potash, tartrate of soda and potash, citrate of potash, citrate of soda, and citrate of magnesia, the last three being more rarely employed than the others. In virtue of what particular properties, it may be asked, have these salts been found to be more serviceable cathartics than other similar salts without specific action, as, for example, the chloride of sodium and the acetate of potash? It is certainly not on account of any difference in their solubility as compared with other simple salines. Nor can it be entirely due to their being more irritant than other salts towards living tissues, and, therefore, towards the intestinal

mucous membrane. This is an important point, for if the supposition as to the purgative secretion being an inflammatory exudation and the result of irritation were correct, the more irritant salt would be the better purgative. Yet chloride of sodium, although a weaker purgative than sulphate of soda or sulphate of magnesia, is a much stronger irritant. I have more than once injected a solution of chloride of sodium into the loop of a cat's intestine, and observed that it invariably caused considerable reddening and inflammation of the mucous membrane of the loop, and that a large amount of albumen was present in the secretion; whereas a solution of an ordinary purgative salt of the same, or even twice the same, strength caused no redness whatever. The irritant character of the purgative salts cannot, therefore, at any rate wholly account for their peculiar action.

I am strongly inclined to believe that the particular character of a saline cathartic, which enables it so much more powerfully than non-purgative salts to produce such an impression on the intestinal mucosa as to reflexly excite the Lieberkühnian gland, is its *bitterness.* It is remarkable that all the most powerful saline cathartics have a well-marked bitter taste. The most active of all of them is probably sulphate of magnesia, and it is the most bitter. It is a common statement in all text-books on materia medica that this salt is not so bitter as sulphate of soda. This is a decided error, for I have made solutions of equal strength of both salts, and have tasted them and asked several of my friends to taste them, and the verdict has invariably been, that the magnesia salt is distinctly more bitter than the soda salt. The sulphate of potash and the neutral alkaline tartrates and double tartrates have all an undoubtedly bitter taste. The phosphate of soda is the only one of the more prominent saline cathartics which forms an exception, and it is well known that it is considerably less powerful than the others. None of the other simple alkaline salts which have not been found to act as efficient purgatives are bitter, as the chlorides, the acetates, and the nitrates. It is generally believed that other secretions of the alimentary canal are strongly excited by bitter substances, and why not also the succus entericus? A bitter substance in the mouth certainly stimulates the salivary flow more strongly that a purely irritant substance; and therapeutists avail themselves

every day of the commonly accepted opinion that bitters increase the gastric secretion. The bitterness, therefore, of a saline cathartic is probably one important factor in its action. But it cannot be the sole factor, whose possession distinguishes a purgative from a non-purgative salt; for why does such a salt as phosphate of soda, which is practically devoid of bitterness, act at all as a cathartic? It is not that this salt is more irritant than the others. It is probably less irritant. This salt would therefore seem to own some other property which renders it purgative. That property has hitherto been believed to be the high endosmotic power of the salt. And there are many who ascribe the action, in part or entirely, of all saline cathartics to their strong endosmotic action. I have already expressed myself as opposed to this view of the mode of the purgative action of the salt, but as I have not as yet given all my reasons for doing so I shall now state them.

In the first place, were the purgative action of the salt entirely or mainly dependent on its endosmotic power, the salt with the highest endosmotic equivalent would be the best purgative. Aubert and Buchheim, to whose experiments I have already referred,[1] have clearly proved that this is not the case. The endosmotic equivalent of certain salts, or the quantity of water which the salt solution gains for every one part of the salt which it loses when separated from water by a parchment or other septum, was found by Aubert to be as follows:[2]—

	Endosmotic Equivalent of	
	Water-free Salt.	Crystalline Salt.
Phosphate of Soda, ...	65	26
Sulphate of Soda, ...	25	11
Sulphate of Potash, ...	15·9	15·9
Rochelle Salt, ...	12·2	9
Sulphate of Magnesia, . . .	8	4
Acetate of Potash, ...	6·5	6·5
Cloride of Sodium, ...	2·7	2·7

If these equivalents be multiplied by the purgative dose of each salt the resulting numbers ought to be nearly equal, if the view be correct that the cathartic activity of the salt depends on its

[1] *Supra*, p. 3. [2] Aubert, *op. cit.*

endosmotic power. Aubert has furnished us with such a calculation:—

Phosphate of Soda,	1035
Sulphate of Soda,	750
Rochelle Salt,	297
Sulphate of Potash,	277
Acetate of Potash,	204
Sulphate of Magnesia,	132
Chloride of Sodium,	40

I do not quite agree with Aubert in the dose he has assigned to each salt. But even were the dose modified, it would not impair the general conclusion, which cannot fail to be drawn from these experiments, that the endosmotic power of a salt is no measure of its cathartic activity, and that, therefore, endosmosis can at most play only a subsidiary part in promoting the outflow of the purgative secretion. Sulphate of magnesia, the most energetic of all the saline purges, has a very low endosmotic equivalent.

Another reason for distrusting the endosmotic theory is to be found in the B. Series of experiments of this investigation. Attention was there drawn to the fact that, when a 20 per cent. solution of sulphate of soda was injected, much more fluid was secreted, and yet much less salt absorbed, than when a 10 per cent. solution was used. According to the present theory the more fluid there was secreted the more salt there ought to be absorbed. The experiments of Series D. are also strongly opposed to this theory.

My final reason for discrediting the endosmotic theory is based upon an experiment which I made to determine the pressure at which the purgative secretion was poured out into the intestine.

Experiment CXXII.—Cat, male, weighing 3·14 kilogrammes, was anæsthetised, and its small intestine was exposed by a mesial abdominal incision in the usual manner. A loop was formed on the intestine by two ligatures about 15 cm. apart, and there was injected into the loop as much of a 20 per cent. solution of sulphate of soda as sufficed to gently distend it. Into the end of the loop was then inserted the end of a tube filled with the same solution and communicating with a mercurial manometer. Care was taken that no fluid escaped at the junction of the tube with the intestine, or at any

other part of the loop or the apparatus. The stimulation of the distension at first caused considerable contractions of the loop, but these after ten minutes cease to occur, and the actual pressure occasioned by the secretion could then be read off. It varied from 21·0 mm. to 23·5 mm. of mercury, and although the experiment was continued for more than an hour, the pressure was never observed to rise beyond the higher of these readings. It may be interesting, for the sake of comparison, to mention that the pressure at which the bile and pancreatic juice are secreted is from 15 to 17 mm.[1]

I next took a piece of the dried intestine of a cat and filled it with the same solution of sulphate of soda, and connected its interior with a mercurial manometer, and dipped it into a $\frac{3}{4}$ per cent. solution of common salt, as representing the serum of the blood. The pressure of the solution within the intestine rapidly rose to 185 mm., at which pressure the intestine burst.

This experiment, I venture to think, proves very conclusively that the purgative secretion is not the result of the endosmotic action of the salt. For, if it were, how comes it that the pressure of the secretion is so low, and corresponds so closely to the pressure under which other secretions, as the bile and pancreatic juice, are naturally secreted?

If, then, the endosmotic power of a saline cathartic is not a factor in the production of its action, what quality is it of the salt (to return to the question raised) which enables certain of the saline cathartics, although possessed of no bitterness, as phosphate of soda, to act as purgatives? I believe it to be a quality of the salt which, although often existing in the most marked degree in those salts in which the endosmotic power is the strongest, is yet probably in no way related to it. I refer to the greater or less *indiffusibility* of the salt, which is able to help the cathartic effect of the salt, not by aiding the secretion of the purgative fluid, but by hindering the absorption of the fluid after it has been secreted. It is a general statement, accepted even by Aubert and Buchheim, that, other things being equal, the higher the endosmotic power of a salt the greater is its purgative action. But these, and other observers, as Liebig, who maintain that the endosmotic power of the salt can entirely account for its purgative action, have erred in attributing to the endosmotic power what really is due to indiffusibility; and the association of the two qualities in most salts has been to a

[1] Heidenhain, *Hermann's Hdbch. d. Physiologie*, Bd. v.

certain extent the cause of their error. Graham has left us the results of many valuable experiments on the diffusibility of salts, and on looking over these I find that all the purgative salts belong to the less diffusible groups.[1] Phosphate of soda is the most indiffusible; sulphate of magnesia comes next, and at some distance below it stand the alkaline tartrates, which are succeeded by the sulphate of soda and sulphate of potash, and still further down by the alkaline chlorides and nitrates. The order, therefore, of the diffusibility of these salts, although it roughly corresponds to that of their endosmotic power, by no means exactly agrees with it. For the sulphate of magnesia is much more indiffusible than sulphate of soda, and yet is much less highly endosmotic. At the same time, allowing for the varying degrees of bitterness possessed by the salt, this order much more closely corresponds to that of the purgative value of the salts. Indeed, were the bitterness of each salts expressed in degrees, and this multiplied by the number representing the diffusibility of the salt, and the product finally multiplied by the dose, a number would be obtained which, omitting the salts possessing any purely irritant action, would be nearly constant for all the purgative salts.

If it be granted that the greater indiffusibility of a salt is to be associated with an increased purgative effect, it is necessary to inquire in what particular manner this quality of the salt operates. It cannot affect the stimulation of the secretion; it must act solely by hindering the absorption of the secreted fluid. We can readily understand how the salt, being on account of its indiffusibility slowly absorbed by the mucous membrane, presents a mechanical hindrance to the water in which it is dissolved. But does it exert merely a mechanical effect, or in addition, is the indiffusibility of the saline cathartic associated with a stronger attraction between the salt and the water of its solution than exists between other more diffusible and non-purgative salts and water? In the theory of saline purgation advanced as the result of the first experiments of this investigation, but which I have now abandoned, I distinctly assumed the existence of such an attraction or union. The same assump

[1] Graham, *Chemical and Physical Researches*, edited by Dr. Angus Smith, Edin., 1876.

tion has been made by several previous observers, among whom Buchheim[1] has put it to experimental test by exposing to moist air equal quantities of several salts, purgative and non-purgative and ascertaining after several days their increase in weight. He found that the less diffusible or purgative salts absorbed on the whole less water than the more diffusible or non-purgative salts, and he therefore obtained from this experiment no proof of the correctness of his assumption. The method, however, is admittedly faulty.

I have also made an experiment with the same object as Buchheim, and although by a different and more satisfactory method, yet with practically the same results. I made 10 per cent. solutions of a number of purgative and non-purgative

TABLE SHOWING RATE OF EVAPORATION OF 10 PER CENT. SOLUTIONS OF CERTAIN CRYSTALLINE SALTS.

Inside Diameter of Tube.		1·60 cm.	1·82 cm.	1·83 cm.	1·82 cm.	1·81 cm.	1·84 cm.	1·81 cm.
Date.	Hour of Observation.	Chloride of Sodium.	Chloride of Sodium.	Acetate of Soda.	Sulphate of Soda.	Phosphate of Soda.	Sulphate of Magnesia.	Tartrate of Soda and Potash.
		cm.	cm.	cm.	cm.	cm.	cm.	cm.
Aug. 31	1.30 p.m.	17	17	17	17	17	17	17
Sept. 7	,, ,,	16·40	16·35	16·40	16·45	16·40	16·40	16·40
,, 15	,, ,,	16·00	15·90	16·00	15·90	15·90	15·90	15·90
,, 23	,, ,,	15·60	15·45	15·60	15·45	15·50	15·50	15·45
,, 27	2.10 ,,	15·40	15·30	15·35	15·30	15·30	15·30	15·30
	Sulphuric acid renewed.							
Oct. 5	12.35 ,,	15·15	15·05	15·05	14·95	15·00	15·05	14·95
,, 13	1.30 ,,	14·90	14·80	14·85	14·75	14·70	14·75	14·70
,, 21	5.15 ,,	14·70	14·50	14·60	14·50	14·45	14·55	14·50
Nov. 1	1.30 ,,	14·32	14·25	14·22	14·15	14·00	14·20	14·15
,, ,,	2.30[2] ,,	14·40	14·27	14·22	14·25	14·25	14·25	14·15

salines, and placed them in glass tubes of nearly equal and of perfectly uniform diameter, standing exactly vertically, and arranged in a circle round a large open beaker containing strong sulphuric acid. The whole was covered with a glass bell-jar well sealed to a ground glass plate, so that there was no

[1] Buchheim, *Beiträge z. Lehre v. d. Endosmose*, &c., Archiv. f. physiolog. Heilkunde, 1853, S. 217.

[2] These readings were made after a slight crystalline efflorescence, which had formed inside the upper empty part of the tube, had been scraped down into the solution.

communication with the outer atmosphere. The tubes were carefully graduated by lineal measurement, not according to capacity, and were filled to an equal height with the various solutions. Daily observations of the decrease of the fluids were made for over a period of two months. The room in which the tubes were placed was kept at a tolerably uniform temperature throughout the experiment. In the foregoing table I give, with one or two exceptions, every eighth observation.

A second solution of chloride of sodium, it will be observed, was placed in a tube a little narrower than the others, in order that I might be able to calculate what effect the unavoidable small variations in the diameters of the other tubes might have on the rate of evaporation.

The result of the experiment was, as can be readily seen, that evaporation proceeds with an almost equal rate in all the saline solutions, and that, therefore, in so far as the affinity of salts for water can be tested by this method, the affinity of the purgative salts is not greater than that of non-purgative salts. That a salt does, however, diminish the rate of evaporation of the water with which it is dissolved—a fact long recognised—is shown in this experiment by the rate of evaporation gradually diminishing, as the salt solution becomes more concentrated. This was not due to the sulphuric acid beginning to lose its hygroscopic action on account of its becoming saturated with moisture, for, even after the renewal of the acid, the rate of evaporation still continues to diminish.

As the method which I employed for testing the affinity of salts for water is, like Buchheim's, not without many objections, I have had recourse to another method, and, without further experiment, have availed myself of its results as found in the researches of Berthelot,[1] Thomsen, and others, which have recently been welded by the first of these into a new system of chemistry under the name of Mécanique Chimique. These chemists measure the strength of affinity between two substances by estimating the amount of heat developed when they are mixed together. Now, most of the hydrated crystalline salts when dissolved in water, instead of evolving heat, absorb it. This has long been known, and some measurements of the degree of cold

[1] Berthelot, *Mécanique Chimique*, Paris, 1879.

were made by Favre and Silbermann; but it is to the more recent investigators that we are indebted for more exact and reliable results. If the evolution of heat be evidence of attraction, absorption of it can hardly be otherwise regarded than as indicating repulsion; and the greater the absorption of heat the greater will be the degree of repulsion. Judged by this view of their thermo-dynamics, the purgative and less diffusible salts, owing to their absorbing a large amount of heat when dissolved in water, are those which repel water most, and in this respect the phosphate of soda acts the most energetically of all the purgative soda salts; whereas the non-purgative and less diffusible salts, as the chlorides, because they dissolve in water with a small absorption of heat, repel water the least. Instead, therefore, of there being a greater affinity between purgative or less diffusible salts and water, there is a less affinity than between water and non-purgative or more diffusible salts.

Clearly, then, the only way in which a highly indiffusible salt, as phosphate of soda, can retard the absorption of the intestinal fluid in the course of purgation, is by the presence of its slowly absorbable molecules mechanically hindering the free absorption of the molecules of the water in which it is dissolved. Molecules of both the salt and water lie in contact with the surface of the mucous membrane; those of the former, on account of their being very slowly removed by absorption, prevent the ready access of those of the latter to the absorptive cells of the membrane. In this manner, therefore the less diffusible salts can, *cæteris paribus,* purge more powerfully than those more diffusible.

I have now discussed the two properties to which I believe the greater activity of certain salts within the intestines is due, and which therefore constitute these salts cathartics, as distinguished from other allied salts, which, although not devoid of purgative action, yet do not act so powerfully as the cathartic salts proper. These two properties are bitterness and slow diffusibility, the one promoting secretion, the other impeding absorption. But whilst the possession of these properties may explain why certain salts are pre-eminently cathartic, it does not explain why other allied salts, as the alkaline chlorides and acetates, although devoid of bitterness and easily diffusible,

nevertheless excite more or less secretion when directly injected into the intestine, or purge when administered by the mouth in a sufficiently large dose. Doubtless the strongly irritant action of many of these salts, as chloride of sodium and nitrate of potassium, is sufficient to account for their purgative action; but there are others of them, as acetate of potash, which cannot be said to be more irritant than the ordinary saline cathartics. It is therefore probable, indeed certain, that all salts, apart from their being bitter and without that they cause visible redness or inflammation of the mucous membrane, can, if sufficiently concentrated, stimulate the mucous membrane of the intestine, when brought into contact with it, and reflexly provoke the intestinal glands to action; if for no other reason that that, on account of their concentration, they abstract water from the epithelial cells on the mucous surface, and thus, by disturbing the cell-protoplasm, affect the sensory nerve filaments, which terminate in or around the protoplasm. This very simple and purely physical effect is probably the basis of the action of every salt, if sufficiently concentrated, on living tissue, and, in this particular instance, of the purgative and non-purgative salines alike, or what might be more strictly termed, the more purgative and the less purgative. In the former the stimulant action of this property is increased by the bitterness, and the purgative effect aided by the slow diffusibility of the salt.

It is also to be remembered that the changes, by way of decomposition, which certain of the saline cathartics undergo in their passage through the alimentary canal, may materially promote their action. The splitting up of a portion of the sulphates of magnesia and soda in the intestines, with the absorption of the disengaged sulphuric acid, will probably result in the residual base uniting with the carbonic acid of the intestinal secretion to form a carbonate or bicarbonate, which, on account of its being less diffusible and less capable of absorption than the corresponding sulphate, will increase the purgative action of the salt. The return of the original acid of the salt to the intestine, as indicated in the experiments of Series D., taking place, as it evidently does (Experiments CXVI. and CXVII., Series H.), to a small extent in proportion to the

amount of the base still within the intestine, will not entirely break up the carbonate formed. Beyond this, I do not believe, and therefore in opposition to Headland, that the absorption and after excretion of the acid of the salt affects its purgative action. The absorbed portion of the salt in the process of its excretion probably plays no part in stimulating the intestinal secretion. My reasons for holding this opinion I have already stated.[1]

In considering the properties which render certain salts cathartics, I have assumed that the salts possess no *specific* stimulating action on the enteric glands, as do those of nearly all the heavier metals. In this I may not be altogether accurate, for whilst it may be held as almost indisputably proved that the salts of soda have no such action, otherwise there would be evidence of it when they are injected in purgative doses into the blood, yet the salts of potash or magnesia may possess it in some degree, as, owing to their highly poisonous effect when injected directly into the circulation, it is impossible to inject them in a quantity approaching a purgative dose. If they do possess a specific purgative action, it must be to a very limited extent, for the still more poisonous salts of the heavier metals rarely fail to excite purgation when introduced into the blood in less even than a lethal dose.

In treating of the nature or mode of production of the purgative secretion by the salt, I have omitted all references to the effect being produced by the action of the salt on any portion of the body outside the nervous and glandular structures of the intestine, for the simple reason that the application of the salt *per se* to any other portion of the body, either by intravenous or by subcutaneous injection, completely fails to cause purgation. I do not, however, deny the possibility of the local intestinal action being controlled by some nervous influence originating in a separate portion of the organism, and altogether independent of the action of the salt. The influence may be such as either to increase the purgative action or to lessen it, and these results it may effect by altering the rate either of secretion or of absorption in the intestine. For example, I have shown in Experiments XLI. and XLII. that irritation by

[1] *Supra*, p. 110.

ligatures of a portion of the intestine distant from the part in which the salt is acting, diminishes the purgative action by promoting secretion. This effect probably does not take place through a purely intra-intestinal nerve mechanism; a much more extended nerve-tract is in all probability involved, consisting at least of the mesenteric nerves and ganglia. Also, according to H. C. Wood, division of the vagi in the neck prevents purgative action by arresting the intestinal secretion. I have not, however, succeeded in observing this inhibitory effect when a saline cathartic was employed.[1]

The intestinal secretion is also affected by subcutaneous irritation in the region of the abdomen (Series of Experiments F.), and there can hardly be any doubt that either in a normal condition, or when stimulated by a purgative, it may be largely affected by many nervous influences, emotional and otherwise.

V. *The Action of the Salt on the Peristaltic Movements of the Intestines.*

The determining whether the salt stimulates these movements is of somewhat less interest, since I have in the course of this investigation removed all uncertainty as to the salt exciting secretion. In the historical sketch at the commencement of this paper, I have remarked how that the German pharmacologists are inclined to regard such a stimulation as the principal, or at least an important, cause of the catharsis. The experiments of Aubert, and Buchheim and Wagner, but more particularly those of Thiry and Radziejewski, form the basis of this belief, without that any of their experiments offer direct proof of increased peristalsis. Legros and Onimus,[2] and Van Braam Houckgeest,[3] have, however, by direct experiment, demonstrated that a saline

[1] Since writing the earlier part of this paper, in which Wood's experiments are shortly commented on, I have had the opportunity of perusing a detailed account of his experiments in the *American Journal of Medical Sciences*, vol. lx. p. 75. I find that he does not attribute the effect of the division of the vagi to any direct influence exerted by these nerves on the secretion of the intestines, but to the accumulation of carbonic acid in the blood and congestion of the portal circulation, caused by the division of the vagi. The shorter account of his experiments, which I had previously read, does not give the same explanation of the action of the divided vagi, and I have, therefore, felt it incumbent to make this correction.

[2] *Op. cit.* [3] *Op. cit.*

purgative, on the contrary, does not stimulate the movements of the intestines. The fitness of the methods employed by the latter observers, and the care with which their experiments were conducted, command acquiescence in their conclusions. In all those of my own experiments in which the intestines were exposed, although I frequently made observation of the peristalsis, I could never on any occasion satisfy myself that it was increased during the action of the salt. I observed, however, in an experiment specially instituted, that moderate distension of the intestine with what may be regarded as the blandest of all ordinary fluids, a $\frac{3}{4}$ per cent. solution of common salt of the same temperature as the body, excited regular contractions of the intestinal wall of the distended loop, which ceased immediately on removal of the pressure. Although, therefore, the salt does not directly stimulate the peristaltic movements of the intestines, yet it is highly probable that it indirectly does so by distending the intestines with the abundantly poured-out secretion. Increased peristalsis may, accordingly, be a subsidiary factor in the action of a saline cathartic, but certainly it is not an essential factor.

B. The Effect of the Saline Cathartic on Other Parts of the Body than the Alimentary System.

As the action of the salt on the circulation and urinary secretion has already been fully discussed to the extent my experiments warrant, and under separate chapters, I shall do no more here than briefly recapitulate the conclusions already arrived at.

I. *The Effect on the Blood and Circulation.*

The salt, by exciting a profuse intestinal secretion, removes, under all circumstances, a large amount of fluid from the blood. If the salt is administered in very dilute solution, the water of the solution by absorption replaces the water of the blood removed by secretion. But if the solution of the salt is concentrated, little or no replacement occurs, and the total bulk of the blood in the body becomes greatly diminished. This concentration of the blood lasts, however, only for one or two hours, because by the end of that time the blood recoups itself from the fluids of the tissues. The action, therefore, of a diluted dose of a saline cathartic on the blood, and secondarily on the

tissue fluids, is considerably different from that of a concentrated dose. The use of the latter would seem to be strongly indicated in the treatment of many forms of dropsy where it is desired to obtain a rapid and powerful reduction of the dropsical fluid. I have already made such an application of it, and with the happiest results.[1]

The profuse intestinal secretion removes with it a large amount of the salts of the blood, but apparently very little of the organic matter, and this will occur whether the solution of the salt administered be concentrated or dilute, although the more free absorption in the latter case will restore a certain proportion of the secreted salts. But if the blood thus loses a portion of its natural salts, its inorganic matter is increased by the presence of the absorbed salt, more of the acid of which than of the base would appear to enter the blood.

A saline cathartic causes, therefore, a partial depletion of the blood—partial, in so far as it only removes a portion of the inorganic constituents, and more or less of the water, along with a mere trace of the dissolved and unformed organic matter, and, unlike an ordinary surgical depletion, removes none of the formed constituents or corpuscular element.

After the purgative action of the salt is at an end, at any rate in so far as the blood is concerned, the diuretic action of the absorbed salt, which is now established, or rather permitted to become apparent, causes a second concentration of the blood, considerably less in degree than the first, but continuing throughout a much longer period. This concentration is probably not characteristic of purgative salts solely, but is also to be observed after the administration of the ordinary diuretic salts.

The presence of the salt in the blood, and its contact with the various tissues and organs, does not, so far as I have been able to make out, affect to any appreciable extent the metabolism of the body.

As regards the effect of the salt on the circulation of the blood, the salt appears to increase the blood-pressure by causing a contraction of the smaller arteries and the capillaries, merely, as I believe, on account of its mildly stimulating the tunica intima of the vessels as it circulates with the blood.

[1] *Lancet*, April 21, 1883.

II. *The Effect on the Urinary Secretion.*

The immediate effect of the administration of the salt is, as in the case of the blood, somewhat dependent on the degree of concentration of the blood. If the solution of the salt is concentrated, and the blood, therefore, rendered also concentrated, the urinary secretion is at first diminished. If, on the other hand, the solution is very dilute, the secretion may be increased by the blood and kidneys removing the excess of water from the intestine. In both cases, after some hours, and, probably after the salt has ceased to exert any active purgative effect, the secretion increases, and a veritable diuresis would appear to be established and to continue for nearly a day.

The salt produces no material alteration of the composition of the urine, beyond that due to its own presence. In the case of sulphate of magnesia, I have proved that much more of the acid of the salt than of the base appears in the urine. This may also occur to a certain extent with other purgative salts.

These are the main results of this lengthy investigation of the physiological action of saline cathartics; and although they have mainly been obtained from experiments with sulphate of soda, and in a few instances sulphate of magnesia, yet these salts are sufficiently typical of the whole group of saline cathartics as to perfectly justify the belief that, had other members of the group been employed, similar results would have been procured. I have to a certain extent pointed out the differences in manner of action which distinguish some of them. They all tolerably closely agree in the ultimate effect they have on the alimentary canal and the body generally. They cause no irritation or inflammation of the canal; stimulate but in the smallest degree the secretion of the more important digestive juices, as the gastric, the pancreatic, and the biliary; have under ordinary circumstances little action on the blood; and mainly act by increasing the intestinal secretion and by hindering the absorption of the intestinal fluid. Their purgative action is, therefore, extremely simple. They sweep out the contents of the alimentary canal with the least possible disturbance of the digestive system and of the other systems of the organism. Few

other purgatives, if any, have so simple an action. The value, therefore, which has long been assigned to them in the treatment of the occasional disturbances of digestion, to which almost every one is at times subject, and where the indication seems to be to empty the canal "cito, tuto, et jucunde," is quite justified by the results of this investigation.

This is a long research and has involved much labour. It was commenced in the laboratory of the Pharmacological Institute at Strassburg under the superintendence of Professor Schmiedeberg, where most of the experiments of the A. series were made. I have already acknowledged my indebtedness to Professor Schmiedeberg for his valuable and kindly help in the carrying out of these experiments. As I did not altogether feel assured of the correctness of the theory of the mode of action of saline cathartics, to which the results of these experiments seemed to lead, I reopened the investigation, after my return to Edinburgh, in the laboratory of the Pharmacological Department of this University, where nearly all the experiments of the remaining series were conducted. Here I have received valuable assistance from many friends; and for such, more than to any other, do I feel grateful to Professor Thomas R. Fraser, but for whose kindness and indulgence the research could not have been continued. I have also to warmly thank Dr J. R. Logan, Dr Hosack Fraser, Dr. J. O. Liddell, Dr. J. H. Balfour, and Mr. James Stewart, who on certain occasions, and sometimes at considerable inconvenience to themselves, have kindly given me their help.

Summary of the Results of this Investigation.

1. A saline purgative always excites more or less secretion from the alimentary canal, depending on the amount of the salt and the strength of its solution, and varying with the nature of the salt.

2. The excito-secretory action of the salt is probably due to the bitterness as well as to the irritant and specific properties of the salt, and not to osmosis.

3. The low diffusibility of the salt impedes the absorption of the secreted fluid.

4. Between stimulated secretion on the one hand, and impeded absorption on the other, there is an accumulation of fluid in the canal.

5. The accumulated fluid, partly from ordinary dynamical laws, partly from a gentle stimulation of the peristaltic movements excited by distension, reaches the rectum and produces purgation.

6. Purgation will not ensue if water be withheld from the diet for one or two days previous to the administration of the salt in a concentrated form.

7. The absence of purgation is not due to the want of water in the alimentary canal, but to its deficiency in the blood.

8. Under ordinary conditions, with an unrestricted supply of water, the maximal amount of fluid accumulated within the canal corresponds very nearly to the quantity of water required to form a 5 or 6 per cent. solution of the amount of salt administered.

9. If, therefore, a solution of this strength be given, it does not increase in bulk.

10. If a solution of greater strength be administered, it rapidly increases in volume until the maximum is attained. This it accomplishes in the case of a 20 per cent. solution in from one to one and a half hours.

11. After the maximum has been reached, the fluid begins gradually and slowly to diminish in quantity.

12. *Cœteris paribus*, the weaker, or in other words, the more voluminous the solution of the salt administered is, the more quickly is the maximum within the canal reached; and accordingly purgation follows with greater rapidity.

13. Unless the solution of the salt is more concentrated than 10 per cent. it excites little or no secretion in the stomach.

14. The salt is absorbed with extreme slowness by the stomach of the cat.

15. The salt excites an active secretion in the intestines, and probably for the most part in the small intestine, all portions of this viscus being capable of yielding the secretion in almost equal quantities.

16. The bile and pancreatic juice participate but very little in the secretion.

17. The secretion is probably a true *succus entericus*, re-

sembling the secretion obtained by Moreau after division of the mesenteric nerves.

18. The secretion is promoted by local irritation of the intestine, as by ligatures, but only in the immediate vicinity of the irritation.

19. Absorption by the intestine generally is reflexly stimulated by such irritation (the effect of numerous ligatures applied at points remote from the seat of the injected salt being to diminish the amount of purgative fluid by accelerated absorption).

20. If the salt solution be injected directly into the small intestine, the stronger within certain limits the solution is, the greater will be the accumulation of fluid within the intestine.

21. This difference is not observed when the salt is administered *per os*, as the strong solution becomes diluted in the stomach and duodenum before passing into the intestine generally,

22. The difference is due to the local action of the salt on the mucous membrane, and probably more to an impeded absorption than to a stimulated secretion.

23. When the salt is administered in the usual manner, it appears, in the case of the sulphate of magnesia and sulphate of soda, to become split up in the small intestine, the acid being more rapidly absorbed than the base.

24. A portion of the absorbed acid shortly afterwards returns to the intestines.

25. After the maximum of excretion of the acid has been reached, the salt begins very slowly and gradually to disappear by absorption, which is checked only by the occurrence of purgation.

26. During the alternations of absorption and secretion of the acid, it is the salt left within the intestine which excites secretion, the absorbed and excreted acid exerting no such action whilst in the blood, or during the process of its excretion, as Headland believed.

27. The salt does not purge when injected into the blood, and excites no intestinal secretion.

28. Nor does it purge, when injected subcutaneously, unless in virtue of its causing local irritation of the abdominal subcutaneous tissue, which acts reflexly on the intestines, dilating

their blood-vessels, and perhaps stimulating their muscular movements.

29. The sulphate of soda exhibits no poisonous action when injected into the circulation.

30. The sulphate of magnesia is, on the other hand, powerfully toxic when so injected, paralysing first the respiration and afterwards the heart, and abolishing sensation or paralysing the sensory-motor reflex centres.

31. Both salts, when administered in the usual manner, produce a gradual but well-marked increase in the tension of the pulse.

32. According as the salt-solution within the intestine increases in amount, there occurs a corresponding diminution of the fluids of the blood.

33. The blood recoups itself in a short time by absorbing from the tissues a nearly equal quantity of their fluids.

34. The salt, after some hours, causes diuresis, and with it a second concentration of the blood, which continues so long as the diuresis is active.

35. As the intestinal secretion excited by the salt contains a very small proportion of organic matter as compared with the inorganic matter, the purgative removes more of the latter than the former from the blood. In certain cases a large quantity of the salts of the blood is thus evacuated.

36. The amount of the normal constituents of the urine is not affected by the salt.

37. After the administration of sulphate of magnesia much more of the acid than of the base is excreted in the urine.

38. The salt has no specific action in lowering the internal temperature of the body, or has it only to a very small extent.

39. It reduces, however, the absolute amount of heat in the body.

Pharmacological Laboratory,
Edinburgh, *June* 1883.

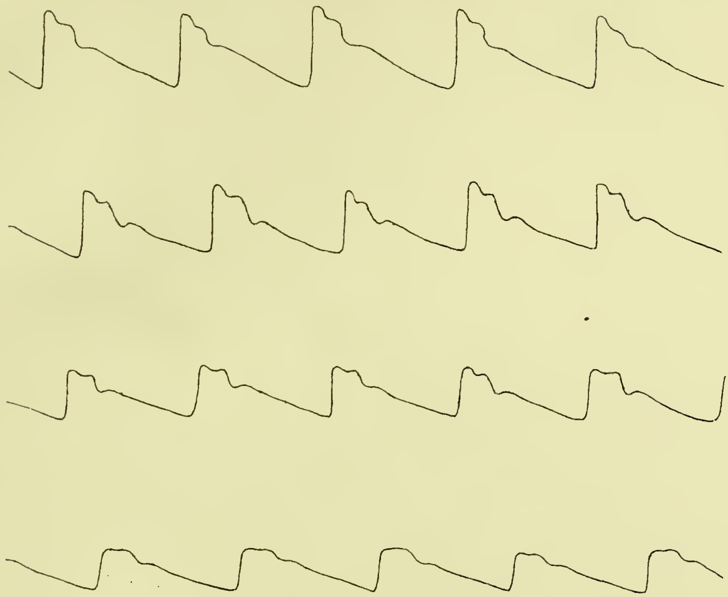
Exper. CXII.

A.

B.

C.

D.



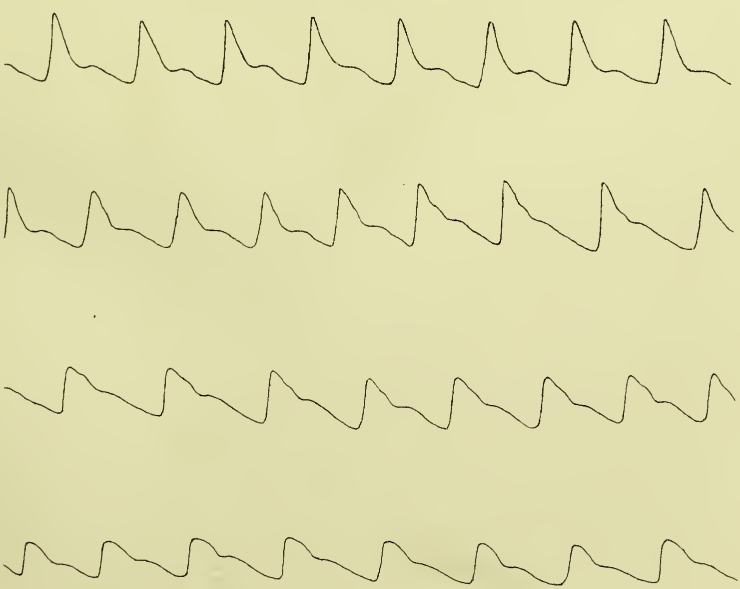
Exper. CXIV.

I.

II.

III.

IV.



F. Huth, Lith.^r Edin.^r